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(54) Title: A METHOD FOR EXTRACTING QUANTITATIVE INFORMATION RELATING TO AN INFLUENCE ON A CELLULAR RESPONSE

(57) Abstract

Cells are genetically modified to expresss a luminophore, e.g., a modified (F64L, S65T, Y66H) Green Fluorescent Protein (GFP, EGFP) coupled to a component of an intracellular signalling pathway such as a transcription factor, a cGMP- or cAMP-dependent protein kinase, a cyclin-, calmodulin- or phospholipid-dependent or mitogen-activated serine/threonin protein kinase, a tyrosine protein kinase, or a protein phosphatase (e.g. PKA, PKC, Erk, Smad, VASP, actin, p38, Jnk1, PKG, IkappaB, CDK2, Grk5, Zap70, p85, protein-tyrosine phosphatase 1C, Stat5, NFAT, NFkappaB, RhoA, PKB). An influence modulates the intracellular signalling pathway in such a way that the luminophore is being redistributed or translocated with the component in living cells in a manner experimentally determined to be correlated to the degree of the influence. Measurement of redistribution is performed by recording of light intensity, fluorescence lifetime, polarization, wavelength shift, resonance energy transfer, or other properties by an apparatus consisting of e.g. a fluorescence microscope and a CCD camera. Data stored as digital images are processed to numbers representing the degree of redistribution. The method can be used as a screening program for identifying a compound that modulates a component and is capable of treating a disease related to the function of the component.

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A METHOD for extracting quantitative information relating to an influence on a cellular response

FIELD OF INVENTION

The present invention relates to a method and tools for extracting quantitative information relating to an influence, on a cellular response, in particular an influence caused by contacting or incubating the cell with a substance influencing a cellular response, where the cellular response is manifested in redistribution of at least one component in the cell. In particular, the invention relates to a method for extracting quantitative information relating to an influence on an intracellular pathway involving redistribution of at least one component associated with the pathway. The method of the invention may be used as a very efficient procedure for testing or discovering the influence of a substance on a physiological process, for example in connection with screening for new drugs, testing of substances for toxicity, identifying drug targets for known or novel drugs. Other valuable uses of the method and technology of the invention will be apparent to the skilled person on the basis of the following disclosure. In a particular embodiment of the invention, the present invention relates to a method of detecting intracellular translocation or redistribution of biologically active polypeptides, preferably an enzyme, affecting intracellular processes, and a DNA construct and a cell for use in the method.

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BACKGROUND OF THE INVENTION

Intracellular pathways are tightly regulated by a cascade of components that undergo modulation in a temporally and spatially characteristic manner. Several disease states can be attributed to altered activity of individual signalling components (i.e. protein kinases, protein phosphatases, transcription factors). These components therefore render themselves as attractive targets for therapeutic intervention.

Protein kinases and phosphatases are well described components of several intracellular signalling pathways. The catalytic activity of protein kinases and phosphatases are assumed to play a role in virtually all regulatable cellular processes. Although the involvement of protein kinases in cellular signalling and regulation have been subjected to extensive studies, detailed knowledge on e.g. the exact timing and spatial characteristics of signalling events is often difficult to obtain due to lack of a convenient technology.

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Novel ways of monitoring specific modulation of intracellular pathways in intact, living cells is assumed to provide new opportunities in drug discovery, functional genomics, toxicology, patient monitoring etc.

The spatial orchestration of protein kinase activity is likely to be essential for the high degree of specificity of individual protein kinases. The phosphorylation mediated by protein kinases is balanced by phosphatase activity. Also within the family of phosphatases translocation has been observed, e.g. translocation of PTP2C to membrane ruffles [(Cossette et al. 1996)], and likewise is likely to be indicative of phosphatase activity.

Protein kinases often show a specific intracellular distribution before, during and after activation. Monitoring the translocation processes and/or redistribution of individual protein kinases or subunits thereof is thus likely to be indicative of their functional activity. A connection between translocation and catalytic activation has been shown for protein kinases like the diacyl glycerol (DAG)-dependent protein kinase C (PKC), the cAMP-dependent protein kinase (PKA) [(DeBernardi et al. 1996)] and the mitogen-activated-protein kinase Erk-1 [(Sano et al. 1995)].

Commonly used methods of detection of intracellular localisation/activity of protein kinases and phosphatases are immunoprecipitation, Western blotting and immunocytochemical detection.

Taking the family of diacyl glycerol (DAG)-dependent protein kinase Cs (PKCs) as an example, it has been shown that individual PKC isoforms that are distributed among different tissues and cells have different activator requirements and undergo differential translocation in response to activation. Catalytically inactive DAG-dependent PKCs are generally distributed throughout the cytoplasm, whereas they upon activation translocate to become associated with different cellular components, e.g. plasma membrane [(Farese, 1992),(Fulop Jr. et al. 1995)] nucleus [(Khalil et al. 1992)], cytoskeleton [(Blobe et al. 1996)]. The translocation phenomenon being indicative of PKC activation has been monitored using different approaches: a) immunocytochemistry where the localisation of individual isoforms can be detected after permeabilisation and fixation of the cells [(Khalil et al. 1992)]; and b) tagging all DAG-dependent PKC isoforms with a fluorescently labelled phorbol myristate acetate (PMA) [(Godson et al. 1996)]; and c) chemical tagging PKC b1 with the fluorophore Cy3 [(Bastiaens & Jovin 1996)] and d) genetic tagging of PKCα ([Schmidt et al. 1997]) and of PKCγ and PKC ε([Sakai et al. 1996]). The first method does not provide dynamic information whereas the latter methods will. Tagging PKC with fluorescently labelled phorbol myristate acetate cannot

distinguish between different DAG-dependent isoforms of PKC but will label and show movement of all isoforms. Chemical and genetic labelling of specific DAG-dependent PKCs confirmed that they in an isoform specific manner upon activation move to cell periphery or nucleus.

In an alternative method, protein kinase A activity has been measured in living cells by chemical labelling one of the kinase's subunit (Adams *et al.*1991). The basis of the methodology is that the regulatory and catalytic subunit of purified protein kinase A is labelled with fluorescein and rhodamine, respectively. At low cAMP levels protein kinase A is assembled in a heterotetrameric form which enables fluorescence resonance energy transfer between the two fluorescent dyes. Activation of protein kinase A leads to dissociation of the complex, thereby eliminating the energy transfer. A disadvantage of this technology is that the labelled protein kinase A has to be microinjected into the cells of interest. This highly invasive technique is cumbersome and not applicable to large scale screening of biologically active substances. A further disadvantage of this technique as compared to the presented invention is that the labelled protein kinase A cannot be inserted into organisms/animals as a transgene.

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Recently it was discovered that Green Fluorescent Protein (GFP) expressed in many different cell types, including mammalian cells, became highly fluorescent [(Chalfie et al. 1994)]. WO95/07463 describes a cell capable of expressing GFP and a method for detecting a protein of interest in a cell based on introducing into a cell a DNA molecule having DNA sequence encoding the protein of interest linked to DNA sequence encoding a GFP such that the protein produced by the DNA molecule will have the protein of interest fused to the GFP, then culturing the cells in conditions permitting expression of the fused protein and detecting the location of the fluorescence in the cell, thereby localizing the protein of interest in the cell. However, examples of such fused proteins are not provided, and the use of fusion proteins with GFP for detection or quantitation of translocation or redistribution of biologically active polypeptides affecting intracellular processes upon activation, such as proteins involved in signalling pathways, e.g. protein kinases or phosphatases, has not been suggested. WO 95/07463 further describes cells useful for the detection of molecules, such as hormones or heavy metals, in a biological sample, by operatively linking a regulatory element of the gene which is affected by the molecule of interest to a GFP, the presence of the molecules will affect the regulatory element which in turn will affect the expression of the GFP. In this way the gene encoding GFP is used as a reporter gene in a cell which is constructed for monitoring the presence of a specific molecular identity.

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Green Fluorescent Protein has been used in an assay for the detection of translocation of the glucocorticoid receptor (GR) [Carey, KL et al., The Journal of Cell Biology, Vol. 133, No. 5, p. 985-996 (1996)]. A GR-S65TGFP fusion has been used to study the mechanisms involved in translocation of the glucocorticoid receptor (GR) in response to the agonist dexamethasone from the cytosol, where it is present in the absence of a ligand, through the nuclear pore to the nucleus where it remains after ligand binding. The use of a GR-GFP fusion enables real-time imaging and quantitation of nuclear/cytoplasmic ratios of the fluorescence signal.

Many currently used screening programmes designed to find compounds that affect protein kinase activity are based on measurements of kinase phosphorylation of artificial or natural 10 substrates, receptor binding and/or reporter gene expression.

DISCLOSURE OF THE INVENTION

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The present invention provides an important new dimension in the investigation of cellular systems involving redistribution in that the invention provides quantification of the redistribution responses or events caused by an influence, typically contact with a chemical substance or mixture of chemical substances, but also changes in the physical environment. The quantification makes it possible to set up meaningful relationships, expressed numerically, or as curves or graphs, between the influences (or the degree of influences) on cellular systems and the redistribution response. This is highly advantageous because, as has been found, the quantification can be achieved in both a fast and reproducible manner, and - what is perhaps even more important - the systems which become quantifiable utilizing the method of the invention are systems from which enormous amounts of new information and insight can be derived.

The present screening assays have the distinct advantage over other screening assays, 25 e.g., receptor binding assays, enzymatic assays, and reporter gene assays, in providing a system in which biologically active substances with completely novel modes of action, e.g. inhibition or promotion of redistribution/translocation of a biologically active polypeptide as a way of regulating its action rather than inhibition/activation of enzymatic activity, can be identified in a way that insures very high selectivity to the particular isoform of the biologically active polypeptide and further development of compound selectivity versus other isoforms of

the same biologically active polypeptide or other components of the same signalling pathway.

In its broadest aspect, the invention relates to a method for extracting quantitative information relating to an influence on a cellular response, the method comprising recording variation, caused by the influence on a mechanically intact living cell or mechanically intact living cells, in spatially distributed light emitted from a luminophore, the luminophore being present in the cell or cells and being capable of being redistributed in a manner which is related with the degree of the influence, and/or of being modulated by a component which is capable of being redistributed in a manner which is related to the degree of the influence, the association resulting in a modulation of the luminescence characteristics of the luminophore, detecting and recording the spatially distributed light from the luminophore, and processing the recorded variation in the spatially distributed light to provide quantitative information correlating the spatial distribution or change in the spatial distribution to the degree of the influence. In a preferred embodiment of the invention the luminophore, which is present in the cell or cells, is capable of being redistributed by modulation of an intracellular pathway, in a manner which is related to the redistribution of at least one component of the intracellular pathway. In another preferred embodiment of the invention, the luminophore is a fluorophore.

The cells

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In the invention the cell and/or cells are mechanically intact and alive throughout the experiment. In another embodiment of the invention, the cell or cells is/are fixed at a point in time after the application of the influence at which the response has been predetermined to be significant, and the recording is made at an arbitrary later time.

The mechanically intact living cell or cells could be selected from the group consisting of fungal cell or cells, such as a yeast cell or cells; invertebrate cell or cells including insect cell or cells; and vertebrate cell or cells, such as mammalian cell or cells. This cell or these cells is/are incubated at a temperature of 30°C or above, preferably at a temperature of from 32°C to 39°C, more preferably at a temperature of from 35°C to 38°C, and most preferably at a temperature of about 37°C during the time period over which the influence is observed. In one aspect of the invention the mechanically intact living cell is part of a matrix of identical or non-identical cells.

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A cell used in the present invention should contain a nucleic acid construct encoding a fusion polypeptide as defined herein and be capable of expressing the sequence encoded by the construct. The cell is a eukaryotic cell selected from the group consisting of fungal cells, such as yeast cells; invertebrate cells including insect cells; vertebrate cells such as mammalian cells. The preferred cells are mammalian cells.

In another aspect of the invention the cells could be from an organism carrying in at least one of its component cells a nucleic acid sequence encoding a fusion polypeptide as defined herein and be capable of expressing said nucleic acid sequence. The organism is selected from the group consisting of unicellular and multicellular organisms, such as a mammal.

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The luminophore

The luminophore is the component which allows the redistribution to be visualised and/or recorded by emitting light in a spatial distribution related to the degree of influence. In one embodiment of the invention, the luminophore is capable of being redistributed in a manner which is physiologically relevant to the degree of the influence. In another embodiment, the luminophore is capable of associating with a component which is capable of being redistributed in a manner which is physiologically relevant to the degree of the influence. In another embodiment, the luminophore correlation between the redistribution of the luminophore and the degree of the influence could be determined experimentally. In a preferred aspect of the invention, the luminophore is capable of being redistributed in substantially the same manner as the at least one component of an intracellular pathway. In yet another embodiment of the invention, the luminophore is capable of being quenched upon spatial association with a component which is redistributed by modulation of the pathway, the quenching being measured as a change in the intensity of the luminescence.

The luminophore could be a fluorophore. In a preferred embodiment of the invention, the luminophore could be a polypeptide encoded by and expressed from a nucleotide sequence harboured in the cell or cells. The luminophore could be a hybrid polypeptide comprising a fusion of at least a portion of each of two polypeptides one of which comprises a luminescent polypeptide and the other one of which comprises a biologically active polypeptide, as defined herein.

The luminescent polypeptide could be a GFP as defined herein or could be selected from the group consisting of green fluorescent proteins having the F64L mutation as defined herein

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such as F64L-GFP, F64L-Y66H-GFP, F64L-S65T-GFP, and EGFP. The GFP could be N- or C-terminally tagged, optionally via a peptide linker, to the biologically active polypeptide or a part or a subunit thereof. The fluorescent probe could be a component of a intracellular signalling pathway. The probe is coded for by a nucleic acid construct.

The pathway of investigation in the present invention could be an intracellular signalling pathway.

The influence

In a preferred embodiment of the invention, the influence could be contact between the mechanically intact living cell or the group of mechanically intact living cells with a chemical substance and/or incubation of the mechanically intact living cell or the group of mechanically intact living cells with a chemical substance. The influence will modulate the intracellular processes. In one aspect the modulation could be an activation of the intracellular processes. In another aspect the modulation could be an deactivation of the intracellular processes. In yet another aspect, the influence could inhibit or promote the redistribution without directly affecting the metabolic activity of the component of the intracellular processes.

In one embodiment the invention is used as a basis for a screening program, where the effect of unknown influences such as a compound library, can be compared to influence of known reference compounds under standardised conditions.

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The recording

In addition to the intensity, there are several parameters of fluorescence or luminescence which can be modulated by the effect of the influence on the underlying cellular phenomena, and can therefore be used in the invention. Some examples are resonance energy transfer, fluorescence lifetime, polarisation, wavelength shift. Each of these methods requires a particular kind of filter in the emission light path to select the component of the light desired and reject other components. The recording of property of light could be in the form of an ordered array of values such as a CCD array or a vacuum tube device such as a vidicon tube.

In one embodiment of the invention, the spatially distributed light emitted by a luminophore could be detected by a change in the resonance energy transfer between the luminophore and another luminescent entity capable of delivering energy to the luminophore, each of

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which has been selected or engineered to become part of, bound to or associated with particular components of the intracellular pathway. In this embodiment, either the luminophore or the luminescent entity capable of delivering energy to the luminophore undergoes redistribution in response to an influence. The resonance energy transfer would be measured as a change in the intensity of emission from the luminophore, preferably sensed by a single channel photodetector which responds only to the average intensity of the luminophore in a non-spatially resolved fashion.

In one embodiment of the invention, the recording of the spatially distributed light could be made at a single point in time after the application of the influence. In another embodiment, the recording could be made at two points in time, one point being before, and the other point being after the application of the influence. The result or variation is determined from the change in fluorescence compared to the fluorescence measured prior to the influence or modulation. In another embodiment of the invention, the recording could be performed at a series of points in time, in which the application of the influence occurs at some time after the first time point in the series of recordings, the recording being performed, e.g., with a predetermined time spacing of from 0.1 seconds to 1 hour, preferably from 1 to 60 seconds, more preferably from 1 to 30 seconds, in particular from 1 to 10 seconds, over a time span of from 1 second to 12 hours, such as from 10 seconds to 12 hours, e.g., from 10 seconds to one hour, such as from 60 seconds to 30 minutes or 20 minutes. The result or variation is determined from the change in fluorescence over time. The result or variation could also be determined as a change in the spatial distribution of the fluorescence over time.

Apparatus

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The recording of spatially distributed luminescence emitted from the luminophore is performed by an apparatus for measuring the distribution of fluorescence in the cell or cells, and thereby any change in the distribution of fluorescence in the cell or cells, which includes at a minimum the following component parts: (a) a light source, (b) a method for selecting the wavelength(s) of light from the source which will excite the fluorescence of the protein, (c) a device which can rapidly block or pass the excitation light into the rest of the system, (d) a series of optical elements for conveying the excitation light to the specimen, collecting the emitted fluorescence in a spatially resolved fashion, and forming an image from this fluorescence emission, (e) a bench or stand which holds the container of the cells being measured in a predetermined geometry with respect to the series of optical elements, (f) a detector to

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record the spatially resolved fluorescence in the form of an image, (g) a computer or electronic system and associated software to acquire and store the recorded images, and to compute the degree of redistribution from the recorded images.

In a preferred embodiment of the invention the apparatus system is automated. In one embodiment the components in d and e mentioned above comprise a fluorescence microscope. In one embodiment the component in f mentioned above is a CCD camera.

In one embodiment the image is formed and recorded by an optical scanning system.

In one embodiment a liquid addition system is used to add a known or unknown compound to any or all of the cells in the cell holder at a time determined in advance. Preferably, the liquid addition system is under the control of the computer or electronic system. Such an automated system can be used for a screening program due to its ability to generate results from a larger number of test compounds than a human operator could generate using the apparatus in a manual fashion.

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The recording of the variation or result with respect to light emitted from the luminophore is performed by recording the spatially distributed light as one or more digital images, and the processing of the recorded variation to reduce it to one or more numbers representative of the degree of redistribution comprises a digital image processing procedure or combination of digital image processing procedures. The quantitative information which is indicative of the degree of the cellular response to the influence or the result of the influence on the intracellular pathway is extracted from the recording or recordings according to a predetermined calibration based on responses or results, recorded in the same manner, to known degrees of a relevant specific influence. This calibration procedure is developed according to principles described below (Developing an Image-based Assay Technique). Specific descriptions of the procedures for particular assays are given in the examples.

While the stepwise procedure necessary to reduce the image or images to the value representative of the is particular to each assay, the individual steps are generally well-known methods of image processing. Some examples of the individual steps are point operations such as subtraction, ratioing, and thresholding, digital filtering methods such as smoothing, sharpening, and edge detection, spatial frequency methods such as Fourier filtering, image cross-correlation and image autocorrelation, object finding and classification (blob analysis),

and colour space manipulations for visualisation. In addition to the algorithmic procedures, heuristic methods such as neural networks may also be used.

Nucleic acid constructs

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- The nucleic acid constructs used in the present invention encode in their nucleic acid sequences fusion polypeptides comprising a biologically active polypeptide that is a component of an intracellular signalling pathway, or a part thereof, and a GFP, preferably an F64L mutant of GFP, N- or C-terminally fused, optionally via a peptide linker, to the biologically active polypeptide or part thereof.
- In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a protein kinase or a phosphatase.
 - In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a transcription factor or a part thereof which changes cellular localisation upon activation.
 - In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a protein, or a part thereof, which is associated with the cytoskeletal network and which changes cellular localisation upon activation.
 - In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a protein kinase or a part thereof which changes cellular localisation upon activation.
- In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a serine/threonine protein kinase or a part thereof capable of changing intracellular localisation upon activation.
 - In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a tyrosine protein kinase or a part thereof capable of changing intracellular localisation upon activation.
- In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a phospholipid-dependent serine/threonine protein kinase or a part thereof capable of changing intracellular localisation upon activation.
 - In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a cAMP-dependent protein kinase or a part thereof capable of changing cellular localisation upon activation. In a preferred embodiment the biologically active polypeptide encoded by the nucleic acid construct is a PKAc-F64L-S65T-GFP fusion.

In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a cGMP-dependent protein kinase or a part thereof capable of changing cellular localisation upon activation.

In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a calmodulin-dependent serine/threonine protein kinase or a part thereof capable of changing cellular localisation upon activation.

In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a mitogen-activated serine/threonine protein kinase or a part thereof capable of changing cellular localisation upon activation. In preferred embodiments the biologically active polypeptide encoded by the nucleic acid constructs are an ERK1-F64L-S65T-GFP fusion or an EGFP-ERK1 fusion.

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In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a cyclin-dependent serine/threonine protein kinase or a part thereof capable of changing cellular localisation upon activation.

In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a protein phosphatase or a part thereof capable of changing cellular localisation upon activation.

In one preferred embodiment of the invention the nucleic acid constructs may be DNA constructs.

- In one embodiment the biologically active polypeptide encoded by the nucleic acid construct In one embodiment the gene encoding GFP in the nucleic acid construct is derived from Aequorea victoria. In a preferred embodiment the gene encoding GFP in the nucleic acid construct is EGFP or a GFP variant selected from F64L-GFP, F64L-Y66H-GFP and F64L-S65T-GFP.
- In preferred embodiments of the invention the DNA constructs which can be identified by any of the DNA sequences shown in SEQ ID NO: 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142 or are variants of these sequences capable of encoding the same fusion polypeptide or a fusion polypeptide which is biologically equivalent thereto, e.g. an isoform, or a splice variant or a homologue from another species.

Screening program

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The present invention describes a method that may be used to establish a screening program for the identification of biologically active substances that directly or indirectly affects intracellular signalling pathways and because of this property are potentially useful as medicaments. Based on measurements in living cells of the redistribution of spatially resolved luminescence from luminophores which undergo a change in distribution upon activation or deactivation of an intracellular signalling pathway the result of the individual measurement of each substance being screened indicates its potential biological activity.

In one embodiment of the invention the screening program is used for the identification of a biologically toxic substance as defined herein that exerts its toxic effect by interfering with an intracellular signalling pathway. Based on measurements in living cells of the redistribution of spatially resolved luminescence from luminophores which undergo a change in distribution upon activation or deactivation of an intracellular signalling pathway the result of the individual measurement of each substance being screened indicates its potential biologically toxic activity. In one embodiment of a screening program a compound that modulates a component of an intracellular pathway as defined herein, can be found and the therapeutic amount of the compound estimated by a method according to the method of the invention. In a preferred embodiment the present invention leads to the discovery of a new way of treating a condition or disease related to the intracellular function of a biologically active polypeptide comprising administration to a patient suffering from said condition or disease of an effective amount of a compound which has been discovered by any method according to the invention. In another preferred embodiment of the invention a method is established for identification of a new drug target or several new drug targets among the group of biologically active polypeptides which are components of intracellular signalling pathways.

In another embodiment of the invention an individual treatment regimen is established for the selective treatment of a selected patient suffering from an ailment where the available medicaments used for treatment of the ailment are tested on a relevant primary cell or cells obtained from said patient from one or several tissues, using a method comprising transfecting the cell or cells with at least one DNA sequence encoding a fluorescent probe according to the invention, transferring the transfected cell or cells back the said patient, or culturing the cell or cells under conditions permitting the expression of said probes and exposing it to an array of the available medicaments, then comparing changes in fluorescence patterns or redistribution patterns of the fluorescent probes in the intact living cell or cells to

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detect the cellular response to the specific medicaments (obtaining a cellular action profile), then selecting one or more medicament or medicaments based on the desired activity and acceptable level of side effects and administering an effective amount of these medicaments to the selected patient.

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Back-tracking of a signal transduction pathway

The present invention describes a method that may be used to establish a screening program for back-tracking signal transduction pathways as defined herein. In one embodiment the screening program is used to establish more precisely at which level one or several compounds affect a specific signal transduction pathway by successively or in parallel testing the influence of the compound or compounds on the redistribution of spatially resolved luminescence from several of the luminophores which undergo a change in distribution upon activation or deactivation of the intracellular signalling pathway under study.

15 Construction and testing of probes

In general, a probe, i.e. a "GeneX"-GFP fusion or a GFP-"GeneX" fusion, is constructed using PCR with "GeneX"-specific primers followed by a cloning step to fuse "GeneX" in frame with GFP. The fusion may contain a short vector derived sequence between "GeneX" and GFP (e.g. part of a multiple cloning site region in the plasmid) resulting in a peptide linker between "GeneX" and GFP in the resulting fusion protein.

Detailed stepwise procedure:

- Identifying the sequence of the gene. This is most readily done by searching a depository of genetic information, e.g. the GenBank Sequence Database, which is widely available and routinely used by molecular biologists. In the specific examples below the GenBank Accession number of the gene in question is provided.
- Design of gene-specific primers. Inspection of the sequence of the gene allows design of gene-specific primers to be used in a PCR reaction. Typically, the top-strand primer encompasses the ATG start codon of the gene and the following ca. 20 nucleotides, while the bottom-strand primer encompasses the stop codon and the ca. 20 preceding nucleotides, if

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the gene is to be fused behind GFP, i.e. a GFP-"GeneX" fusion. If the gene is to be fused in front of GFP, i.e. a "GeneX"-GFP fusion, a stop codon must be avoided. Optionally, the full length sequence of GeneX may not be used in the fusion, but merely the part which localizes and redistributes like GeneX in response to a signal.

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In addition to gene-specific sequences, the primers contain at least one recognition sequence for a restriction enzyme, to allow subsequent cloning of the PCR product. The sites are chosen so that they are unique in the PCR product and compatible with sites in the cloning vector. Furthermore, it may be necessary to include an exact number of nucleotides between the restriction enzyme site and the gene-specific sequence in order to establish the correct reading frame of the fusion gene and/or a translation initiation consensus sequence. Lastly, the primers always contain a few nucleotides in front of the restriction enzyme site to allow efficient digestion with the enzyme.

- -Identifying a source of the gene to be amplified. In order for a PCR reaction to produce a product with gene-specific primers, the gene-sequence must initially be present in the reaction, e.g. in the form of cDNA. Information in GenBank or the scientific literature will usually indicate in which tissue(s) the gene is expressed, and cDNA libraries from a great variety of tissues or cell types from various species are commercially available, e.g. from Clontech
 (Palo Alto), Stratagene (La Jolla) and Invitrogen (San Diego). Many genes are also available in cloned form from The American Type Tissue Collection (Virginia).
 - Optimizing the PCR reaction. Several factors are known to influence the efficiency and specificity of a PCR reaction, including the annealing temperature of the primers, the concentration of ions, notably Mg²⁺ and K⁺, present in the reaction, as well as pH of the reaction. If the result of a PCR reaction is deemed unsatisfactory, it might be because the parameters mentioned above are not optimal. Various annealing temperatures should be tested, e.g. in a PCR machine with a built-in temperature gradient, available from e.g. Stratagene (La Jolla), and/or various buffer compositions should be tried, e.g. the OptiPrime buffer system from Stratagene (La Jolla).

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- Cloning the PCR product. The vector into which the amplified gene product will be cloned and fused with GFP will already have been taken into consideration when the primers were designed. When choosing a vector, one should at least consider in which cell types the probe subsequently will be expressed, so that the promoter controlling expression of the probe is compatible with the cells. Most expression vectors also contain one or more selective markers, e.g. conferring resistance to a drug, which is a useful feature when one wants to make stable transfectants. The selective marker should also be compatible with the cells to be used.
- The actual cloning of the PCR product should present no difficulty as it typically will be a one-step cloning of a fragment digested with two different restriction enzymes into a vector digested with the same two enzymes. If the cloning proves to be problematic, it may be because the restriction enzymes did not work well with the PCR fragment. In this case one could add longer extensions to the end of the primers to overcome a possible difficulty of digestion close to a fragment end, or one could introduce an intermediate cloning step not based on restriction enzyme digestion. Several companies offer systems for this approach, e.g. Invitrogen (San Diego) and Clontech (Palo Alto).
 - Once the gene has been cloned and, in the process, fused with the GFP gene, the resulting product, usually a plasmid, should be carefully checked to make sure it is as expected. The most exact test would be to obtain the nucleotide sequence of the fusion-gene.

Testing the probe

Once a DNA construct for a probe has been generated, its functionality and usefulness may be tested by subjecting it to the following tests:

- Transfecting it into cells capable of expressing the probe. The fluorescence of the cell is inspected soon after, typically the next day. At this point, two features of cellular fluorescence are noted: the intensity and the sub-cellular localization.

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The intensity should usually be at least as strong as that of unfused GFP in the cells. If it is not, the sequence or quality of the probe-DNA might be faulty, and should be carefully checked.

The sub-cellular localization is an indication of whether the probe is likely to perform well. If it 5 localizes as expected for the gene in question, e.g. is excluded from the nucleus, it can immediately go on to a functional test. If the probe is not localized soon after the transfection procedure, it may be because of overexpression at this point in time, as the cell typically will have taken of very many copies of the plasmid, and localization will occur in time, e.g. within a few weeks, as plasmid copy number and expression level decreases. If localization does 10 not occur after prolonged time, it may be because the fusion to GFP has destroyed a localization function, e.g. masked a protein sequence essential for interaction with its normal cellular anchor-protein. In this case the opposite fusion might work, e.g. if GeneX-GFP does not work, GFP-GeneX might, as two different parts of GeneX will be affected by the proximity to GFP. If this does not work, the proximity of GFP at either end might be a problem, and it 15 could be attempted to increase the distance by incorporating a longer linker between GeneX and GFP in the DNA construct.

If there is no prior knowledge of localization, and no localization is observed, it may be because the probe should not be localized at this point, because such is the nature of the protein fused to GFP. It should then be subjected to a functional test.

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In a functional test, the cells expressing the probe are treated with at least one compound known to perturb, usually by activating, the signalling pathway on which the probe is expected to report by redistributing itself within the cell. If the redistribution is as expected, e.g. if prior knowledge tell that it should translocate from location X to location Y, it has passed the first critical test. In this case it can go on to further characterization and quantification of the response.

If it does not perform as expected, it may be because the cell lacks at least one component of the signalling pathway, e.g. a cell surface receptor, or there is species incompatibility, e.g. if the probe is modelled on sequence information of a human geneproduct, and the cell is of hamster origin. In both instances one should identify other cell types for the testing process where these potential problems would not apply.

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If there is no prior knowledge about the pattern of redistribution, the analysis of the redistribution will have to be done in greater depth to identify what the essential and indicative features are, and when this is clear, it can go on to further characterization and quantification of the response. If no feature of redistribution can be identified, the problem might be as mentioned above, and the probe should be retested under more optimal cellular conditions.

If the probe does not perform under optimal cellular conditions it's back to the drawing board.

Developing an image-based assay technique

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The process of developing an image-based redistribution assay begins with either the unplanned experimental observation that a redistribution phenomenon can be visualised, or the design of a probe specifically to follow a redistribution phenomenon already known to occur. In either event, the first and best exploratory technique is for a trained scientist or technician to observe the phenomenon. Even with the rapid advances in computing technology, the human eye-brain combination is still the most powerful pattern recognition system known, and requires no advance knowledge of the system in order to detect potentially interesting and useful patterns in raw data. This is especially if those data are presented in the form of images, which are the natural "data type" for human visual processing. Because human visual processing operates most effectively in a relatively narrow frequency range, i.e., we cannot see either very fast or very slow changes in our visual field, it may be necessary to record the data and play it back with either time dilation or time compression.

Some luminescence phenomena cannot be seen directly by the human eye. Examples include polarization and fluorescence lifetime. However, with suitable filters or detectors, these signals can be recorded as images or sequences of images and displayed to the human in the fashion just described. In this way, patterns can be detected and the same methods can be applied.

Once the redistribition has been determined to be a reproducible phenomenon, one or more data sets are generated for the purpose of developing a procedure for extracting the quantitative information from the data. In parallel, the biological and optical conditions are determined which will give the best quality raw data for the assay. This can become an iterative process; it may be necessary to develop a quantitative procedure in order to assess the effect on the assay of manipulating the assay conditions.

The data sets are examined by a person or persons with knowledge of the biological phenomenon and skill in the application of image processing techniques. The goal of this exercise is to determine or at least propose a method which will reduce the image or sequence of images constituting the record of a "response" to a value corresponding to the degree of the response. Using either interactive image processing software or an image processing toolbox and a programming language, the method is encoded as a procedure or algorithm which takes the image or images as input and generates the degree of response (in any units) as its output. Some of the criteria for evaluating the validity of a particular procedure are:

 Does the degree of the response vary in a biologically significant fashion, i.e., does it show the known or putative dependence on the concentration of the stimulating agent or condition?

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- Is the degree of response reproducible, i.e., does the same concentration or level of stimulating agent or condition give the same response with an acceptable variance?
- Is the dynamic range of the response sufficient for the purpose of the assay? If not,
 can a change in the procedure or one of its parameters improve the dynamic range?
- Does the procedure exhibit any clear "pathologies", i.e., does it give ridiculous values for the response if there are commonly occurring imperfections in the imaging process? Can these pathologies be eliminated, controlled, or accounted for?
- Can the procedure deal with the normal variation in the number and/or size of cells in an image?

In some cases the method may be obvious; in others, a number of possible procedures may suggest themselves. Even if one method appears clearly superior to others, optimisation of parameters may be required. The various procedures are applied to the data set and the criteria suggested above are determined, or the single procedure is applied repeatedly with adjustment of the parameter or parameters until the most satisfactory combination of signal, noise, range, etc. are arrived at. This is equivalent to the calibration of any type of single-channel sensor.

The number of ways of extracting a single value from an image are extremely large, and thus an intelligent approach must be taken to the initial step of reducing this number to a small, finite number of possible procedures. This is not to say that the procedure arrived at is

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necessarily the best procedure - but a global search for the best procedure is simply out of the question due to the sheer number of possibilities involved.

Image-based assays are no different than other assay techniques in that their usefulness is characterised by parameters such as the specificity for the desired component of the sample, the dynamic range, the variance, the sensitivity, the concentration range over which the assay will work, and other such parameters. While it is not necessary to characterise each and every one of these before using the assay, they represent the only way to compare one assay with another.

10 Example: Developing a Quantitative assay for GLUT4 Translocation

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GLUT4 is a member of the class of glucose transporter molecules which are important in cellular glucose uptake. It is known to translocate to the plasma membrane under some conditions of stimulation of glucose uptake. The ability to visualize the glucose uptake response noninvasively, without actually measuring glucose uptake, would be a very useful assay for anyone looking for, for example, treatments for type II diabetes.

A CHO cell line which stably expressed the human insulin receptor was used as the basis for a new cell line which stably expressed a fusion between GLUT4 and GFP. This cell line was expected to show translocation of GLUT4 to the plasma membrane as visualized by the movement of the GFP. The translocation could definitely be seen in the form of the appearance of local increases in the fluorescence in regions of the plasma membrane which had a characteristic shape or pattern. This is shown in Figure 12.

These objects became known as "snircles", and the phenomenon of their appearance as "snircling". In order to quantitate their appearance, a method had to be found to isolate them as objects in the image field, and then enumerate them, measure their area, or determine some parameter about them which correlated in a dose-dependent fashion with the concentration of insulin to which the cells had been exposed. In order to separate the snircles, a binarization procedure was applied in which one copy of the image smoothed with a relatively severe gaussian kernel (sigma = 2.5) was subtracted from another copy to which only a relatively light gaussian smooth had been applied (sigma=0.5). The resultant image was rescaled to its min/max range, and an automatic threshold was applied to divide the image into two levels. The thresholded image contains a background of one value all found object with another value. The found objects were first filtered through a filter to remove objects far too

large and far too small to be snircles. The remaining objects, which represent snircles and other artifacts from the image with approximately the same size and intensity characteristics as snircles, are passed into a classification procedure which has been previously trained with many images of snircles to recognize snircles and exclude the other artifacts. The result of this procedure is a binary image which shows only the found snircles to the degree to which the classification procedure can accurately identify them. The total area of the snircles is then summed and this value is the quantitative measure of the degree of snircling for that image.

10 **Definitions**:

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In the present specification and claims, the term "an influence" covers any influence to which the cellular response comprises a redistribution. Thus, e.g., heating, cooling, high pressure, low pressure, humidifying, or drying are influences on the cellular response on which the resulting redistribution can be quantified, but as mentioned above, perhaps the most important influences are the influences of contacting or incubating the cell or cells with substances which are known or suspected to exert and influence on the cellular response involving a redistribution contribution. In another embodiment of the invention the influence could be substances from a compound drug library.

In the present context, the term "green fluorescent protein" is intended to indicate a protein which, when expressed by a cell, emits fluorescence upon exposure to light of the correct excitation wavelength (cf. [(Chalfie *et al.*1994)]). In the following, GFP in which one or more amino acids have been substituted, inserted or deleted is most often termed "modified GFP". "GFP" as used herein includes wild-type GFP derived from the jelly fish *Aequorea victoria* and modifications of GFP, such as the blue fluorescent variant of GFP disclosed by Heim et al. (1994). Proc.Natl.Acad.Sci. 91:12501, and other modifications that change the spectral properties of the GFP fluorescence, or modifications that exhibit increased fluorescence when expressed in cells at a temperature above about 30°C described in PCT/DK96/00051, published as WO 97/11094 on 27 March 1997 and hereby incorporated by reference, and which comprises a fluorescent protein derived from *Aequorea* Green Fluorescent Protein (GFP) or any functional analogue thereof, wherein the amino acid in position 1 upstream from the chromophore has been mutated to provide an increase of fluorescence intensity when the

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fluorescent protein of the invention is expressed in cells. Preferred GFP variants are F64L-GFP, F64L-Y66H-GFP and F64L-S65T-GFP. An especially preferred variant of GFP for use in all the aspects of this invention is EGFP (DNA encoding EGFP which is a F64L-S65T variant with codons optimized for expression in mammalian cells is available from Clontech, Palo Alto, plasmids containing the EGFP DNA sequence, cf. GenBank Acc. Nos. U55762, U55763).

The term "intracellular signalling pathway" and "signal transduction pathway" are intended to indicate the coordinated intracellular processes whereby a living cell transduce an external or internal signal into cellular responses. Said signal transduction will involve an enzymatic reaction said enzymes include but are not limited to protein kinases, GTPases, ATPases, protein phosphatases, phospholipases. The cellular responses include but are not limited to gene transcription, secretion, proliferation, mechanical activity, metabolic activity, cell death.

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The term "second messenger" is used to indicate a low molecular weight component involved in the early events of intracellular signal transduction pathways.

The term "luminophore" is used to indicate a chemical substance which has the property of emitting light either inherently or upon stimulation with chemical or physical means. This includes but is not limited to fluorescence, bioluminescence, phosphorescence, chemiluminescence.

The term "mechanically intact living cell" is used to indicate a cell which is considered living according to standard criteria for that particular type of cell such as maintenance of normal membrane potential, energy metabolism, proliferative capability, and has not experienced any physically invasive treatment designed to introduce external substances into the cell such as microinjection.

The term "physiologically relevant" ,when applied to an experimentally determined redistribution of an intracellular component, as measured by a change in the luminescence properties or distribution, is used to indicate that said redistribution can be explained in terms of the underlying biological phenomenon which gives rise to the redistribution.

Th terms "image processing" and "image analysis" are used to describe a large family of digital data analysis techniques or combination of such techniques which reduce ordered arrays of numbers (images) to quantitative information describing those ordered arrays of numbers. When said ordered arrays of numbers represent measured values from a physical process, the quantitative information derived is therefore a measure of the physical process.

The term "fluorescent probe" is used to indicate a fluorescent fusion polypeptide comprising a GFP or any functional part thereof which is N- or C-terminally fused to a biologically active polypeptide as defined herein, optionally via a peptide linker consisting of one or more amino acid residues, where the size of the linker peptide in itself is not critical as long as the desired functionality of the fluorescent probe is maintained. A fluorescent probe according to the invention is expressed in a cell and basically mimics the physiological behaviour of the biologically active polypeptide moiety of the fusion polypeptide.

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The term "mammalian cell" is intended to indicate any living cell of mammalian origin. The cell may be an established cell line, many of which are available from The American Type Culture Collection (ATCC, Virginia, USA) or a primary cell with a limited life span derived from a mammalian tissue, including tissues derived from a transgenic animal, or a newly established immortal cell line derived from a mammalian tissue including transgenic tissues, or a hybrid cell or cell line derived by fusing different celltypes of mammalian origin e.g. hybridoma cell lines. The cells may optionally express one or more non-native gene products, e.g. receptors, enzymes, enzyme substrates, prior to or in addition to the fluorescent probe. Preferred cell lines include but are not limited to those of fibroblast origin, e.g. BHK, CHO, BALB, or of endothelial origin, e.g. HUVEC, BAE (bovine artery endothelial), CPAE (cow pulmonary artery endothelial) or of pancreatic origin, e.g. RIN, INS-1, MIN6, bTC3, aTC6, bTC6, HIT, or of hematopoietic origin, e.g. adipocyte origin, e.g. 3T3-L1, neuronal/neuroendocrine origin, e.g. AtT20, PC12, GH3, muscle origin, e.g. SKMC, A10, C2C12, renal origin, e.g. HEK 293, LLC-PK1.

The term "hybrid polypeptide" is intended to indicate a polypeptide which is a fusion of at least a portion of each of two proteins, in this case at least a portion of the green fluorescent protein, and at least a portion of a catalytic and/or regulatory domain of a protein kinase. Furthermore a hybrid polypeptide is intended to indicate a fusion polypeptide comprising a

GFP or at least a portion of the green fluorescent protein that contains a functional fluorophore, and at least a portion of a biologically active polypeptide as defined herein provided that said fusion is not the PKC α -GFP, PKC γ -GFP, and PKC ϵ -GFP disclosed by Schmidt et al.and Sakai et al., respectively. Thus, GFP may be N- or C-terminally tagged to a biologically active polypeptide, optionally via a linker portion or linker peptide consisting of a sequence of one or more amino acids. The hybrid polypeptide or fusion polypeptide may act as a fluorescent probe in intact living cells carrying a DNA sequence encoding the hybrid polypeptide under conditions permitting expression of said hybrid polypeptide.

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The term "kinase" is intended to indicate an enzyme that is capable of phosphorylating a cellular component.

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The term "protein kinase" is intended to indicate an enzyme that is capable of phosphorylating serine and/or threonine and/or tyrosine in peptides and/or proteins.

The term "phosphatase" is intended to indicate an enzyme that is capable of dephosphorylating phosphoserine and/or phosphothreonine and/or phosphotyrosine in peptides and/or proteins.

In the present context, the term "biologically active polypeptide" is intended to indicate a polypeptide affecting intracellular processes upon activation, such as an enzyme which is active in intracellular processes or a portion thereof comprising a desired amino acid sequence which has a biological function or exerts a biological effect in a cellular system. In the polypeptide one or several aminoacids may have been deleted, inserted or replaced to alter its biological function, e.g. by rendering a catalytic site inactive. Preferably, the biologically active polypeptide is selected from the group consisting of proteins taking part in an intracellular signalling pathway, such as enzymes involved in the intracellular phosphorylation and dephosphorylation processes including kinases, protein kinases and phosphorylases as defined herein, but also proteins making up the cytoskeleton play important roles in intracellular signal transduction and are therefore included in the meaning of "biologically active polypeptide" herein. More preferably, the biologically active polypeptide is a protein which according to its state as activated or non-activated changes localisation within the cell, preferably as an in-

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termediary component in a signal transduction pathway. Included in this preferred group of biologically active polypeptides are cAMP dependent protein kinase A.

The term "a substance having biological activity" is intended to indicate any sample which has a biological function or exerts a biological effect in a cellular system. The sample may be a sample of a biological material such as a sample of a body fluid including blood, plasma, saliva, milk, urine, or a microbial or plant extract, an environmental sample containing pollutants including heavy metals or toxins, or it may be a sample containing a compound or mixture of compounds prepared by organic synthesis or genetic techniques.

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The phrase "any change in fluorescence" means any change in absorption properties, such as wavelength and intensity, or any change in spectral properties of the emitted light, such as a change of wavelength, fluorescence lifetime, intensity or polarisation, or any change in the intracellular localisation of the fluorophore. It may thus be localised to a specific cellular component (e.g. organelle, membrane, cytoskeleton, molecular structure) or it may be evenly distributed throughout the cell or parts of the cell.

The phrase "back-tracking of a signal transduction pathway" is intended to indicate.

The term "organism" as used herein indicates any unicellular or multicellular organism preferably originating from the animal kingdom including protozoans, but also organisms that are members of the plant kingdoms, such as algae, fungi, bryophytes, and vascular plants are included in this definition.

The term "nucleic acid" is intended to indicate any type of poly- or oligonucleic acid sequence, such as a DNA sequence, a cDNA sequence, or an RNA sequence.

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The term "biologically equivalent" as it relates to proteins is intended to mean that a first protein is equivalent to a second protein if the cellular functions of the two proteins may substitute for each other, e.g. if the two proteins are closely related isoforms encoded by different genes, if they are splicing variants, or allelic variants derived from the same gene, if they perform identical cellular functions in different cell types, or in different species. The term "biologically equivalent" as it relates to DNA is intended to mean that a first DNA sequ-

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ence encoding a polypeptide is equivalent to a second DNA sequence encoding a polypeptide if the functional proteins encoded by the two genes are biologically equivalent.

The phrase "back-tracking of a signal transduction pathway" is intended to indicate a process for defining more precisely at what level a signal transduction pathway is affected, either by the influence of chemical compounds or a disease state in an organism. Consider a specific signal transduction pathway represented by the bioactive polypeptides A - B - C - D, with signal transduction from A towards D. When investigating all components of this signal transduction pathway compounds or disease states that influence the activity or redistribution of only D can be considered to act on C or downstream of C whereas compounds or disease states that influence the activity or redistribution of C and D, but not of A and B can be considered to act downstream of B.

The term "fixed cells" is used to mean cells treated with a cytological fixative such as glutaraldehyde or formaldehyde, treatments which serve to chemically cross-link and stabilize soluble and insoluble proteins within the structure of the cell. Once in this state, such proteins cannot be lost from the structure of the now-dead cell.

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BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. CHO cells expressing the PKAc-F64L-S65T-GFP hybrid protein have been treated in HAM's F12 medium with 50 mM forskolin at 37°C. The images of the GFP fluorescence in these cells have been taken at different time intervals after treatment, which were: a) 40 seconds b) 60 seconds c) 70 seconds d) 80 seconds. The fluorescence changes from a punctate to a more even distribution within the (non-nuclear) cytoplasm.

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Figure 2. Time-lapse analysis of forskolin induced PKAc-F64L-S65T-GFP redistribution. CHO cells, expressing the PKAc-F64L-S65T-GFP fusion protein were analysed by time-lapse fluorescence microscopy. Fluorescence micrographs were acquired at regular intervals from 2 min before to 8 min after the addition of agonist. The cells were challenged with 1 mM forskolin immediately after the upper left image was acquired (t=0). Frames were collected at the following times: i) 0, ii) 1, iii) 2, iv) 3, v) 4 and vi) 5 minutes. Scale bar 10 mm.

Figure 3. Time-lapse analyses of PKAc-F64L-S65T-GFP redistribution in response to various agonists. The effects of 1 mM forskolin (A), 50 mM forskolin (B), 1mM dbcAMP (C) and 100 mM IBMX (D) (additions indicated by open arrows) on the localisation of the PKAc-F64L-S65T-GFP fusion protein were analysed by time-lapse fluorescence microscopy of CHO/PKAc-F64L-S65T-GFP cells. The effect of addition of 10 mM forskolin (open arrow), followed shortly by repeated washing with buffer (solid arrow), on the localisation of the PKAc-F64L-S65T-GFP fusion protein was analysed in the same cells (E). In a parallel experiment, the effect of adding 10 mM forskolin and 100 mM IBMX (open arrow) followed by repeated washing with buffer containing 100 mM IBMX (solid arrow) was analysed (F). Removing forskolin caused PKAc-F64L-S65T-GFP fusion protein to return to the cytoplasmic aggregates while this is prevented by the continued presence of IBMX (F). The effect of 100 nM glucagon (Fig 3G, open arrow) on the localisation of the PKAc-F64L-S65T-GFP fusion protein is also shown for BHK/GR, PKAc-F64L-S65T-GFP cells. The effect of 10 mM norepinephrine (H), solid arrow, on the localisation of the PKAc-F64L-S65T-GFP fusion protein was analysed similarly, in transiently transfected CHO, PKAc-F64L-S65T-GFP cells, pretreated with 10 mM forskolin, open arrow, to increase [cAMP], N.B. in Fig 3H the x-axis counts the image numbers, with 12 seconds between images. The raw data of each experiment consisted of 60 fluorescence micrographs acquired at regular intervals including several images acquired before the addition of buffer or agonist. The charts (A-G) each show a quantification of the response seen through all the 60 images, performed as described in analysis method 2. The change in total area of the highly fluorescent aggregates, relative to the initial area of fluorescent aggregates is plotted as the ordinate in all graphs in Figure 3, versus time for each experiment. Scale bar 10 mm.

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Figure 4. Dose response curve (two experiments) for forskolin-induced redistribution of the PKAc-F64L-S65T-GFP fusion.

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Figure 5. Time from initiation of a response to half maximal (t_{1/2max}) and maximal (t_{max}) PKAc-F64L-S65T-GFP redistribution. The data was extracted from curves such as that shown in "Figure 2." All $t_{1/2\text{max}}$ and t_{max} values are given as mean±SD and are based on a total of 26-30 cells from 2-3 independent experiments for each forskolin concentration. Since the observed redistribution is sustained over time, the t_{max} values were taken as the earliest time point at which complete redistribution is reached. Note that the values do not relate to the degree of redistribution.

Figure 6. Parallel dose response analyses of forskolin induced cAMP elevation and PKAc-15 F64L-S65T-GFP redistribution. The effects of buffer or 5 increasing concentrations of forskolin on the localisation of the PKAc-F64L-S65T-GFP fusion protein in CHO/PKAc-F64L-S65T-GFP cells, grown in a 96 well plate, were analysed as described above. Computing the ratio

of the SD's of fluorescence micrographs taken of the same field of cells, prior to and 30 min after the addition of forskolin, gave a reproducible measure of PKAc-F64L-S65T-GFP redistribution. The graph shows the individual 48 measurements and a trace of their mean±s.e.m at each forskolin concentration. For comparison, the effects of buffer or 8 increasing concentrations of forskolin on [cAMP], was analysed by a scintillation proximity assay of cells grown under the same conditions. The graph shows a trace of the mean ± s.e.m of 4

25 experiments expressed in arbitrary units.

> Figure 7. BHK cells stably transfected with the human muscarinic (hM1) receptor and the PKCa-F64L-S65T-GFP fusion. Carbachol (100 mM added at 1.0 second) induced a transient redistribution of PKCa-F64L-S65T-GFP from the cytoplasm to the plasma membrane. Images were taken at the following times: a) 1 second before carbachol addition, b) 8.8 seconds after addition and c) 52.8 seconds after addition.

Figure 8. BHK cells stably transfected with the hM1 receptor and PKCa-F64L-S65T-GFP fusion were treated with carbachol (1 mM, 10 mM, 100 mM). In single cells intracellular [Ca²+] was monitored simultaneously with the redistribution of PKCa-F64L-S65T-GFP. Dashed line indicates the addition times of carbachol. The top panel shows changes in the intracellular Ca²+ concentration of individual cells with time for each treatment. The middle panel shows changes in the average cytoplasmic GFP fluorescence for individual cells against time for each treatment. The bottom panel shows changes in the fluorescence of the periphery of single cells, within regions that specifically include the circumferential edge of a cell as seen in normal projection, the regions which offers best chance to monitor changes in the fluorescence intensity of the plasma membrane.

Figure 9. a) The hERK1-F64L-S65T-GFP fusion expressed in HEK293 cells treated with 100 mM of the MEK1 inhibitor PD98059 in HAM F-12 (without serum) for 30 minutes at 37 °C. The nuclei empty of fluorescence during this treatment.

- b) The same cells as in (a) following treatment with 10 % foetal calf serum for 15 minutes at 37 $^{\circ}\text{C}$.
- c) Time profiles for the redistribution of GFP fluorescence in HEK293 cells following treatment with various concentrations of EGF in Hepes buffer (HAM F-12 replaced with Hepes buffer directly before the experiment). Redistribution of fluorescence is expressed as the change in the ratio value between areas in nucleus and cytoplasm of single cells. Each time profile is the mean for the changes seen in six single cells.
- d) Bar chart for the end-point measurements, 600 seconds after start of EGF treatments, of fluorescence change (nucleus:cytoplasm) following various concentrations of EGF.

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Figure 10.

- a) The SMAD2-EGFP fusion expressed in HEK293 cells starved of serum overnight in HAM
 F-12. HAM F-12 was then replaced with Hepes buffer pH 7.2 immediately before the experiment. Scale bar is 10 mm.
- 30 b) HEK 293 cells expressing the SMAD2-EGFP fusion were treated with various concentration of TGF-beta as indicated, and the redistribution of fluorescence monitored against time.

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The time profile plots represent increases in fluorescence within the nucleus, normalised to starting values in each cell measured. Each trace is the time profile for a single cell nucleus.

c) A bar chart representing the end-point change in fluorescence within nuclei (after 850 seconds of treatment) for different concentrations of TGF-beta. Each bar is the value for a single nucleus in each treatment.

Figure 11. The VASP-F64L-S65T-GFP fusion in CHO cells stably transfected with the human insulin receptor. The cells were starved for two hours in HAM F-12 without serum, then treated with 10% foetal calf serum. The image shows the resulting redistribution of fluorescence after 15 minutes of treatment. GFP fluorescence becomes localised in structures identified as focal adhesions along the length of actin stress fibres.

Figure 12. Time lapse recording GLUT4-GFP redistribution in CHO-HIR cells. Time indicates minutes after the addition of 100 nM insulin.

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EXAMPLE 1

Construction, testing and implementation of an assay for cAMP based on PKA activation in real time within living cells.

Useful for monitoring the activity of signalling pathways which lead to altered concentrations of cAMP, e.g. activation of G-protein coupled receptors which couple to G-proteins of the $G_{\rm S}$ or $G_{\rm I}$ class.

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The catalytic subunit of the murine cAMP dependent protein kinase (PKAc)was fused C-terminally to a F64L-S65T derivative of GFP. The resulting fusion (PKAc-F64L-S65T-GFP) was used for monitoring *in vivo* the translocation and thereby the activation of PKA.

Construction of the PKAc-F64L-S65T-GFP fusion:

15 Convenient restriction endonuclease sites were introduced into the cDNAs encoding murine PKAc (Gen Bank Accession number: M12303) and F64L-S65T-GFP (sequence disclosed in WO 97/11094) by polymerase chain reaction (PCR). The PCR reactions were performed according to standard protocols with the following primers:

5'PKAc: TTggACACAAgCTTTggACACCCTCAggATATgggCAACgCCgCCgCCGCCAAg (SEQ ID NO:3),

3'PKAc: gTCATCTTCTCgAgTCTTTCAggCgCgCCCAAACTCAgTAAACTCCTTgCCACAC (SEQ ID NO:4) ,

5'GFP: TTggACACAAgCTTTggACACggCgCgCCATgAgTAAAggAgAAGAACTTTTC (SEQ ID NO:1),

25 3'GFP: gTCATCTTCTCgAgTCTTACTCCTgAggTTTgTATAgTTCATCCATgCCATgT (SEQ ID NO:2).

The PKAc amplification product was then digested with HindIII+AscI and the F64L-S65T-GFP product with AscI+XhoI. The two digested PCR products were subsequently ligated with a HindIII+XhoI digested plasmid (pZeoSV® mammalian expression vector, Invitrogen, San Diego, CA, USA). The resulting fusion construct (SEQ ID NO:68 & 69) was under control of the SV40 promoter.

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Transfection and cell culture conditions.

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Chinese hamster ovary cells (CHO), were transfected with the plasmid containing the PKAc-F64L-S65T-GFP fusion using the calcium phosphate precipitate method in HEPES-buffered saline (Sambrook *et al.*, 1989). Stable transfectants were selected using 1000 mg Zeocin/ml (Invitrogen) in the growth medium (DMEM with 1000 mg glucose/l, 10 % fetal bovine serum (FBS), 100 mg penicillin-streptomycin mixture ml⁻¹, 2 mM L-glutamine purchased from Life Technologies Inc., Gaithersburg, MD, USA). Untransfected CHO cells were used as the control. To assess the effect of glucagon on fusion protein translocation, the PKAc-F64L-S65T-GFP fusion was stably expressed in baby hamster kidney cells overexpressing the human glucagon receptor (BHK/GR cells) Untransfected BHK/GR cells were used as the control. Expression of GR was maintained with 500 mg G418/ml (*Neo* marker) andPKAc-F64L-S65T-GFP was maintained with 500 mg Zeocin/ml (*Sh ble* marker). CHO cells were also simultaneously co-transfected with vectors containing the PKAc-F64L-S65T-GFP fusion and the human a2a adrenoceptor (hARa2a).

For fluorescence microscopy, cells were allowed to adhere to Lab-Tek chambered coverglasses (Nalge Nunc Int., Naperville, IL, USA) for at least 24 hours and cultured to about 80% confluence. Prior to experiments, the cells were cultured over night without selection pressure in HAM F-12 medium with glutamax (Life Technologies), 100 mg penicillinstreptomycin mixture ml⁻¹ and 0.3 % FBS. This medium has low autofluorescence enabling fluorescence microscopy of cells straight from the incubator.

Monitoring activity of PKA activity in real time:

Image aquisition of live cells were gathered using a Zeiss Axiovert 135M fluorescence microscope fitted with a Fluar 40X, NA: 1.3 oil immersion objective and coupled to a Photometrics CH250 charged coupled device (CCD) camera. The cells were illuminated with a 100 W HBO arc lamp. In the light path was a 470±20 nm excitation filter, a 510 nm dichroic mirror

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and a 515±15 nm emission filter for minimal image background. The cells were kept and monitored to be at 37°C with a custom built stage heater.

Images were processed and analyzed in the following manner:.

Method 1: Stepwise procedure for quantitation of translocation of PKA:

- The image was corrected for dark current by performing a pixel-by-pixel subtraction of a dark image (an image taken under the same conditions as the actual image, except the camera shutter is not allowed to open).
 - 2. The image was corrected for non-uniformity of the illumination by performing a pixel-by-pixel ratio with a flat field correction image (an image taken under the same conditions as the actual image of a uniformly fluorescent specimen).
 - 3. The image histogram, i.e., the frequency of occurrence of each intensity value in the image, was calculated.
 - 4. A smoothed, second derivative of the histogram was calculated and the second zero is determined. This zero corresponds to the inflection point of the histogram on the high side of the main peak representing the bulk of the image pixel values.
 - 5. The value determined in step 4 was subtracted from the image. All negative values were discarded.
 - 6. The variance (square of the standard deviation) of the remaining pixel values was determined. This value represents the "response" for that image.
- 20 7. Scintillation proximity assay (SPA) for independent quantitation of cAMP:

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Method 2: Alternative method for quantitation of PKA redistribution:

- 1. The fluorescent aggregates are segmented from each image using an automatically found threshold based on the maximisation of the information measure between the object and background. The *a priori* entropy of the image histogram is used as the information measure.
- 2. The area of each image occupied by the aggregates is calculated by counting pixels in the segmented areas.
- 3. The value obtained in step 2 for each image in a series, or treatment pair, is normalised to the value found for the first (unstimulated) image collected. A value of zero (0) indicates no redistribution of fluorescence from the starting condition. A value of one (1) by this method equals full redistribution.
- 15 Cells were cultured in HAM F-12 medium as described above, but in 96-well plates. The medium was exchanged with Ca²⁺-HEPES buffer including 100 mM IBMX and the cells were stimulated with different concentrations of forskolin for 10 min. Reactions were stopped with addition of NaOH to 0.14 M and the amount of cAMP produced was measured with the cAMP-SPA kit, RPA538 (Amersham) as described by the manufacturer.

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Manipulating intracellular levels of cAMP to test the PKAc-F64L-S65T-GFP fusion.

The following compounds were used to vary cAMP levels: Forskolin, an activator of adenylate cyclase; dbcAMP, a membrane permeable cAMP analog which is not degraded by phosphodiesterase; IBMX, an inhibitor of phosphodiesterase.

- 25 CHO cells stably expressing the PKAc-F64L-S65T-GFP, showed a dramatic translocation of the fusion protein from a punctate distribution to an even distribution throughout the cytoplasm following stimulation with 1 mM forskolin (n=3), 10 mM forskolin (n=4) and 50 mM forskolin (n=4) (Fig 1), or dbcAMP at 1mM (n=6).
 - Fig. 2 shows the progression of response in time following treatment with 1 mM forskolin.

Fig. 3 gives a comparison of the average temporal profiles of fusion protein redistribution and a measure of the extent of each response to the three forskolin concentrations (Fig. 3A, E, B), and to 1 mM dbcAMP (fig 3C) which caused a similar but slower response, and to addition of 100 mM IBMX (n=4, Fig. 3D) which also caused a slow response, even in the absence of adenylate cyclase stimulation. Addition of buffer (n=2) had no effect (data not shown).

As a control for the behavior of the fusion protein, F64L-S65T-GFP alone was expressed in CHO cells and these were also given 50 mM forskolin (n=5); the uniform diffuse distribution characteristic of GFP in these cells was unaffected by such treatment (data not shown).

The forskolin induced translocation of PKAc-F64L-S65T-GFP showed a dose-response relationship (Fig 4 and 6), see quantitative procedures above.

Reversibility of PKAc-F64L-S65T-GFP translocation.

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The release of the PKAc probe from its cytoplasmic anchoring hotspots was reversible. Washing the cells repeatedly (5-8 times) with buffer after 10µM forskolin treatment completely restored the punctate pattern within 2-5 min (n=2, Fig. 3E). In fact the fusion protein returned to a pattern of fluorescent cytoplasmic aggregates virtually indistinguishable from that observed before forskolin stimulation.

To test whether the return of fusion protein to the cytoplasmic aggregates reflected a decreased [cAMP], cells were treated with a combination of 10 mM forskolin and 100 mM IBMX (n=2) then washed repeatedly (5-8 times) with buffer containing 100 mM IBMX (Fig. 3F). In these experiments, the fusion protein did not return to its prestimulatory localization after removal of forskolin.

25 Testing the PKA-F64L-S65T-GFP probe with physiologically relevant agents.

To test the probe's response to receptor activation of adenylate cyclase, BHK cells stably transfected with the glucagon receptor and the PKA-F64L-S65T-GFP probe were exposed to glucagon stimulation. The glucagon receptor is coupled to a G_s protein which activates adenylate cyclase, thereby increasing the cAMP level. In these cells, addition of 100 nM glucagon (n=2) caused the release of the PKA-F64L-S65T-GFP probe from the cytoplasmic aggregates and a resulting translocation of the fusion protein to a more even cytoplasmic

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distribution within 2-3 min (Fig. 3G). Similar but less pronounced effects were seen at lower glucagon concentrations (n=2, data not shown). Addition of buffer (n=2) had no effect over time (data not shown).

Transiently transfected CHO cells expressing hARa2a and the PKA-F64L-S65T-GFP probe were treated with 10 mM forskolin for 7.5 minutes, then, in the continued presence of forskolin, exposed to 10 mM norepinephrine to stimulate the exogenous adrenoreceptors, which couple to a G₁ protein, which inhibit adenylate cyclase. This treatment led to reappearance of fluorescence in the cytoplasmic aggregates indicative of a decrease in [cAMP]_i (Fig. 3H).

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Fusion protein translocation correlated with [cAMP],

As described above, the time it took for a response to come to completion was dependent on the forskolin dose (Fig. 5) In addition the degree of responses was also dose dependent. To test the PKA-F64L-S65T-GFP fusion protein translocation in a semi high through-put system, CHO cells stably transfected with the PKA-F64L-S65T-GFP fusion was stimulated with buffer and 5 increasing doses of forskolin (n=8). Using the image analysis algorithm described above (Method 1), a dose response relationship was observed in the range from 0.01-50 mM forskolin (Fig. 6). A half maximal stimulation was observed at about 2 mM forskolin. In parallel, cells were stimulated with buffer and 8 increasing concentrations of forskolin (n=4) in the range 0.01-50 mM. The amount of cAMP produced was measured in an SPA assay. A steep increase was observed between 1 and 5 mM forskolin coincident with the steepest part of the curve for fusion protein translocation (also Fig. 6)

25 EXAMPLE 2

Quantitation of redistribution in real-time within living cells.

Probe for detection of PKC activity in real time within living cells:

Construction of PKC-GFP fusion:

The probe was constructed by ligating two restriction enzyme treated polymerase chain reaction (PCR) amplification products of the cDNA for murine PKC α (GenBank Accession number: M25811) and F64L-S65T-GFP (sequence disclosed in WO 97/11094) respectively. Taq® polymerase and the following oligonucleotide primers were used for PCR;

5'mPKCa: TTggACACAAgCTTTggACACCCTCAggATATggCTgACgTTTACCCggCCAACg (SEQ ID NO:5),

3'mPKCa: gTCATCTTCTCgAgTCTTTCAggCgCgCCCTACTgCACTTTgCAAgATTgggTgC (SEQ ID NO:6),

5'F64L-S65T-GFP: TTggACACAAgCTTTggACACggCgCGCCATgAgTAAAggAgAAGAACTT-TTC (SEQ ID NO:1),

3'F64L-S65T-GFP: gTCATCTTCTCgAgTCTTACTCCTgAggTTTgTATAgTTCATCCATgC-CATgT (SEQ ID NO:2).

The hybrid DNA strand was inserted into the pZeoSV® mammalian expression vector as a HindIII-XhoI casette as described in example 1.

15 Cell Culture:

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BHK cells expressing the human M1 receptor under the control of the inducible metal-lothionine promoter and maintained with the dihydrofolate reductase marker were transfected with the PKC α -F64L-S65T-GFP probe using the calcium phosphate precipitate method in HEPES buffered saline (HBS [pH 7.10]). Stable transfectants were selected using 1000 μ g Zeocin®/ml in the growth medium (DMEM with 1000 mg glucose/l, 10 % foetal bovine serum (FBS), 100 mg penicillin-streptomycin mixture ml-1, 2 mM l-glutamine). The hM1 receptor and PKC α -F64L-S65T-GFP fusion protein were maintained with 500 nM methotrexate and 500 μ g Zeocin®/ml respectively. 24 hours prior to any experiment, the cells were transferred to HAM F-12 medium with glutamax, 100 μ g penicillin-streptomycin mixture ml-1 and 0.3 % FBS. This medium relieves selection pressure, gives a low induction of signal transduction pathways and has a low autofluorescence at the relevant wavelength enabling fluorescence microscopy of cells straight from the incubator.

Monitoring the PKC activity in real time:

Digital images of live cells were gathered using a Zeiss Axiovert 135M fluorescence microscope fitted with a 40X, NA: 1.3 oil immersion objective and coupled to a Photometrics

CH250 charged coupled device (CCD) camera. The cells were illuminated with a 100 W arc lamp. In the light path was a 470±20 nm excitation filter, a 510 nm dichroic mirror and a 515±15 nm emission filter for minimal image background. The cells were kept and monitored to be at 37°C with a custom built stage heater.

5 Images were analyzed using the IPLab software package for Macintosh.

Upon stimulation of the M1-BHK cells, stably expressing the PKC α -F64L-S65T-GFP fusion, with carbachol we observed a dose-dependent transient translocation from the cytoplasm to the plasma membrane (Fig. 7a,b,c). Simultaneous measurement of the cytosolic free calcium concentration shows that the carbachol-induced calcium mobilisation precedes the translocation (Fig. 8).

Stepwise procedure for quantitation of translocation of PKC:

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- 1. The image was corrected for dark current by performing a pixel-by-pixel subtraction of a dark image (an image taken under the same conditions as the actual image, except the camera shutter is not allowed to open).
- 15 2. The image was corrected for non-uniformity of the illumination by performing a pixel-by-pixel ratio with a flat field correction image (an image taken under the same conditions as the actual image of a uniformly fluorescent specimen).
 - 3. A copy of the image was made in which the edges are identified. The edges in the image are found by a standard edge-detection procedure convolving the image with a kernel which removes any large-scale unchanging components (i.e., background) and accentuates any small-scale changes (i.e., sharp edges). This image was then converted to a binary image by threshholding. Objects in the binary image which are too small to represent the edges of cells were discarded. A dilation of the binary image was performed to close any gaps in the image edges. Any edge objects in the image which were in contact with the borders of the image are discarded. This binary image represents the edge mask.
 - 4. Another copy of image was made via the procedure in step 3. This copy was further processed to detect objects which enclose "holes" and setting all pixels inside the holes to the binary value of the edge, i.e., one. This image represents the whole cell mask.
- 5. The original image was masked with the edge mask from step 3 and the sum total of all pixel values is determined.

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- 6. The original image was masked with the whole cell mask from step 4 and the sum total of all pixel values was determined.
- 7. The value from step 5 was divided by the value from step 6 to give the final result, the fraction of fluorescence intensity in the cells which was localized in the edges.

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EXAMPLE 3

Probes for detection of mitogen activated protein kinase Erk1 redistribution.

Useful for monitoring signalling pathways involving MAPK, e.g. to identify compounds which modulate the activity of the pathway in living cells.

Erk1, a serine/threonine protein kinase, is a component of a signalling pathway which is activated by e.g. many growth factors.

Probes for detection of ERK-1 activity in real time within living cells:

- The extracellular signal regulated kinase (ERK-1, a mitogen activated protein kinase, MAPK) is fused N- or C-terminally to a derivative of GFP. The resulting fusions expressed in different mammalian cells are used for monitoring *in vivo* the nuclear translocation, and thereby the activation, of ERK1 in response to stimuli that activate the MAPK pathway.
 - a) Construction of murine ERK1 F64L-S65T-GFP fusion:
- 20 Convenient restriction endonuclease sites are introduced into the cDNAs encoding murine ERK1 (GenBank Accession number: Z14249) and F64L-S65T-GFP (sequence disclosed in WO 97/11094) by polymerase chain reaction (PCR). The PCR reactions are performed according to standard protocols with the following primers:
- 5'ERK1: TTggACACAAgCTTTggACACCCTCAggATATggCggCggCggCggCggCggCTCCgggggggCgggg (SEQ ID NO:7),

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5'F64L-S65T-GFP: TTggACACAAgCTTTggACACggCgCgCCATgAgTAAAggAgAAGAACTT-TTC (SEQ ID NO:1)

5 3'F64L-S65T-GFP: gTCATCTTCTCgAgTCTTACTCCTgAggTTTgTATAgTTCATCCATgC-CATgT (SEQ ID NO:2)

To generate the mERK1-F64L-S65T-GFP (SEQ ID NO:56 & 57) fusion the ERK1 amplification product is digested with HindIII+AscI and the F64L-S65T-GFP product with AscI+XhoI. To generate the F64L-S65T-GFP-mERK1 fusion the ERK1 amplification product is then digested with HindIII+Bsu36I and the F64L-S65T-GFP product with Bsu36I+XhoI. The two pairs of digested PCR products are subsequently ligated with a HindIII+XhoI digested plasmid (pZeoSV® mammalian expression vector, Invitrogen, San Diego, CA, USA). The resulting fusion constructs are under control of the SV40 promoter.

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b) The human Erk1 gene (GenBank Accession number: X60188) was amplified using PCR according to standard protocols with primers Erk1-top (SEQ ID NO:9) and Erk1-bottom/+stop (SEQ ID NO:10). The PCR product was digested with restriction enzymes E-coR1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with EcoR1 and BamH1. This produces an EGFP-Erk1 fusion
 (SEQ ID NO:38 &39) under the control of a CMV promoter.

The plasmid containing the EGFP-Erk1 fusion was transfected into HEK293 cells employing the FUGENE transfection reagent (Boehringer Mannheim). Prior to experiments the cells were grown to 80%-90% confluency 8 well chambers in DMEM with 10% FCS. The cells were washed in plain HAM F-12 medium (without FCS), and then incubated for 30-60 minutes in plain HAM F-12 (without FCS) with 100 micromolar PD98059, an inhibitor of MEK1, a kinase which activates Erk1; this step effectively empties the nucleus of EGFP-Erk1. Just before starting the experiment, the HAM F-12 was replaced with Hepes buffer following a wash with Hepes buffer. This removes the PD98059 inhibitor; if blocking of MEK1 is still wanted (e.g. in control experiments), the inhibitor is included in the Hepes buffer.

The experimental setup of the microscope was as described in example 1.

60 images were collected with 10 seconds between each, and with the test compound added after image number 10.

Addition of EGF (1-100 nM) caused within minutes a redistribution of EGFP-Erk1 from the cytoplasm into the nucleus (Fig. 9a,b).

The response was quantitated as described below and a dose-dependent relationship between EGF concentration and nuclear translocation of EGFP-Erk1 was found (Fig. 9c,d). Reditribution of GFP fluorescence is expressed in this example as the change in the ratio value between areas in nuclear versus cytoplasmic compartments of the cell. Each time profile is the average of nuclear to cytoplasmic ratios from six cells in each treatment.

EXAMPLE 4:

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Probes for detection of Erk2 redistribution.

Useful for monitoring signalling pathways involving MAPK, e.g. to identify compounds which modulate the activity of the pathway in living cells.

Erk2, a serine/threonine protein kinase, is closely related to Erk1 but not identical; it is a component of a signalling pathway which is activated by e.g. many growth factors.

- a) The rat Erk2 gene (GenBank Accession number: M64300) was amplified using PCR according to standard protocols with primers Erk2-top (SEQ ID NO:11) and Erk2-bottom/+stop (SEQ ID NO:13) The PCR product was digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produces an EGFP-Erk2 fusion (SEQ ID NO:40 &41) under the control of a CMV promoter.
- b) The rat Erk2 gene (GenBank Accession number: M64300) was amplified using PCR according to standard protocols with primers (SEQ ID NO:11) Erk2-top and Erk2-bottom/-stop (SEQ ID NO:12). The PCR product was digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and BamH1. This produces an Erk2-EGFP fusion (SEQ ID NO:58 &59) under the control of a CMV promoter.

The resulting plasmids were transfected into CHO cells and BHK cells. The cells were grown under standard conditions. Prior to experiments, the cells were starved in medium without serum for 48-72 hours. This led to a predominantly cytoplasmic localization of both probes, especially in BHK cells. 10% fetal calf serum was added to the cells and the fluorescence of the cells was recorded as explained in example 3. Addition of serum caused the probes to redistribute into the nucleus within minutes of addition of serum.

EXAMPLE 5:

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10 Probes for detection of Smad2 redistribution.

Useful for monitoring signalling pathways activated by some members of the transforming growth factor-beta family, e.g. to identify compounds which modulate the activity of the pathway in living cells.

Smad 2, a signal transducer, is a component of a signalling pathway which is induced by some members of the TGFbeta family of cytokines.

- a) The human Smad2 gene (GenBank Accession number: AF027964) was amplified using PCR according to standard protocols with primers Smad2-top (SEQ ID NO:24) and Smad2-bottom/+stop (SEQ ID NO:26). The PCR product was digested with restriction enzymes E-coR1 and Acc651, and ligated into pEGFP-C1 (Clontech; Palo Alto; GenBank Accession number U55763) digested with EcoR1 and Acc651. This produces an EGFP-Smad2 fusion (SEQ ID NO:50&51) under the control of a CMV promoter.
- b) The human Smad2 gene (GenBank Accession number: AF027964) was amplified using PCR according to standard protocols with primers Smad2-top (SEQ ID NO:24) and Smad2-bottom/-stop (SEQ ID NO:25). The PCR product was digested with restriction enzymes E-coR1 and Acc65I, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with EcoR1 and Acc65I. This produces a Smad2-EGFP fusion (SEQ ID NO:74 &75) under the control of a CMV promoter.
- The plasmid containing the EGFP-Smad2 fusion was transfected into HEK293 cells, where it showed a cytoplasmic distribution. Prior to experiments the cells were grown in 8 well Nunc

chambers in DMEM with 10% FCS to 80% confluency and starved overnight in HAM F-12 medium without FCS.

For experiments, the HAM F-12 medium was replaced with Hepes buffer pH 7.2.

The experimental setup of the microscope was as described in example 1.

90 images were collected with 10 seconds between each, and with the test compound added after image number 5.

After serum starvation of cells, each nucleus contains less GFP fluorescence than the surrounding cytoplasm (Fig. 10a). Addition of TGFbeta caused within minutes a redistribution of EGFP-Smad2 from the cytoplasma into the nucleus (Fig. 10b).

The redistribution of fluorescence within the treated cells was quantified simply as the fractional increase in nuclear fluorescence normalised to the starting value of GFP fluorescence in the nucleus of each unstimulated cell.

15 EXAMPLE 6:

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Probe for detection of VASP redistribution.

Useful for monitoring signalling pathways involving rearrangement of cytoskeletal elements, e.g. to identify compounds which modulate the activity of the pathway in living cells.

VASP, a phosphoprotein, is a component of cytoskeletal structures, which redistributes in response to signals which affect focal adhesions.

a) The human VASP gene (GenBank Accession number: Z46389) was amplified using PCR according to standard protocols with primers VASP-top (SEQ ID NO:94) and VASP-bottom/+stop (SEQ ID NO:95). The PCR product was digested with restriction enzymes Hind3 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Hind3and BamH1. This produces an EGFP-VASP fusion (SEQ ID NO:124 &125) under the control of a CMV promoter.

The resulting plasmid was transfected into CHO cells expressing the human insulin receptor using the calcium-phosphate transfection method. Prior to experiments, cells were grown in 8 well Nunc chambers and starved overnight in medium without FCS.

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Experiments are performed in a microscope setup as described in example 1.

10% FCS was added to the cells and images were collected. The EGFP-VASP fusion was redistributed from a somewhat even distribution near the periphery into more localized structures, identified as focal adhesion points (Fig. 11).

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A large number of further GFP fusions have been made or are in the process of being made, as apparent from the following Examples 7-22 which also suggest suitable host cells and substances for activation of the cellular signalling pathways to be monitored and analyzed.

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EXAMPLE 7:

Probe for detection of actin redistribution.

Useful for monitoring signalling pathways involving rearrangement or formation of actin filaments, e.g. to identify compounds which modulate the activity of pathways leading to cytoskeletal rearrangements in living cells.

Actin is a component of cytoskeletal structures, which redistributes in response to very many cellular signals.

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The actin binding domain of the human alpha-actinin gene (GenBank Accession number: X15804) was amplified using PCR according to standard protocols with primers ABD-top (SEQ ID NO:90) and ABD-bottom/-stop (SEQ ID NO:91). The PCR product was digested with restriction enzymes Hind3 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Hind3 and BamH1. This produced an actin-binding-domain-EGFP fusion (SEQ ID NO:128 &129) under the control of a CMV promoter.

The resulting plasmid was transfected into CHO cells expressing the human insulin receptor. Cells were stimulated with insulin which caused the actin binding domain-EGFP probe to become redistributed into morphologically distinct membrane-associated structures.

Example 8:

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Probes for detection of p38 redistribution.

Useful for monitoring signalling pathways responding to various cellular stress situations, e.g. to identify compounds which modulate the activity of the pathway in living cells, or as a counterscreen.

p38, a serine/thronine protein kinase, is a component of a stress-induced signalling pathway which is activated by many types of cellular stress, e.g. TNFalpha, anisomycin, UV and mitomycin C.

- a) The human p38 gene (GenBank Accession number: L35253) was amplified using PCR according to standard protocols with primers p38-top (SEQ ID NO:14) and p38-bottom/+stop (SEQ ID NO: 16). The PCR product was digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produced an EGFP-p38 fusion (SEQ ID NO:46 &47) under the control of a CMV promoter.
- b) The human p38 gene (GenBank Accession number: L35253) was amplified using PCR according to standard protocols with primers p38-top (SEQ ID NO:13) and p38-bottom/-stop (SEQ ID NO:15). The PCR product was digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and BamH1. This produced a p38-EGFP fusion (SEQ ID NO:64 &65) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. HEK293, in which the
EGFP-p38 probe and/or the p38-EGFP probe should change its cellular distribution from
predominantly cytoplasmic to nuclear within minutes in response to activation of the signalling pathway with e.g. anisomycin.

Example 9:

30 Probes for detection of Jnk1 redistribution.

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Useful for monitoring signalling pathways responding to various cellular stress situations, e.g. to identify compounds which modulate the activity of the pathway in living cells, or as a counterscreen.

Jnk1, a serine/threonine protein kinase, is a component of a stress-induced signalling pathway different from the p38 described above, though it also is activated by many types of cellular stress, e.g. TNFalpha, anisomycin and UV.

- a) The human Jnk1 gene (GenBank Accession number: L26318) was amplified using PCR according to standard protocols with primers Jnk-top (SEQ ID NO:17) and Jnk-bottom/+stop (SEQ ID NO:19). The PCR product was digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produced an EGFP-Jnk1 fusion (SEQ ID NO:44 &45) under the control of a CMV promoter.
- b) The human Jnk1 gene (GenBank Accession number: L26318) was amplified using PCR according to standard protocols with primers Jnk-top (SEQ ID NO:17) and Jnk-bottom/-stop (SEQ ID NO:18). The PCR product was digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and BamH1. This produced a Jnk1-EGFP fusion (SEQ ID NO:62 &63) under the control of a CMV promoter.
- The resulting plasmids are transfected into a suitable cell line, e.g. HEK293, in which the EGFP-Jnk1 probe and/or the Jnk1-EGFP probe should change its cellular distribution from predominantly cytoplasmic to nuclear in response to activation of the signalling pathway with e.g. anisomycin.

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Example 10:

Probes for detection of PKG redistribution.

Useful for monitoring signalling pathways involving changes in cyclic GMP levels, e.g. to identify compounds which modulate the activity of the pathway in living cells.

30 PGK, a cGMP-dependent serine/threonine protein kinase, mediates the guanylyl-cyclase/cGMP signal.

- a) The human PKG gene (GenBank Accession number: Y07512) is amplified using PCR according to standard protocols with primers PKG-top (SEQ ID NO:81) and PKG-bottom/+stop (SEQ ID NO:83) . The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produces an EGFP-PKG fusion (SEQ ID NO:134 &135) under the control of a CMV promoter.
- b) The human PKG gene (GenBank Accession number: Y07512) is amplified using PCR according to standard protocols with primers PKG-top (SEQ ID NO:81) and PKG-bottom/-stop (SEQ ID NO: 82). The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and BamH1. This produces a PKG-EGFP fusion (SEQ ID NO:136 &137) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. A10, in which the EGFP-PKG probe and/or the PKG-EGFP probe should change its cellular distribution from cytoplasmic to one associated with cytoskeletal elements within minutes in response to treatment with agents which raise nitric oxide (NO) levels.

Example 11:

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- 20 Probes for detection of IkappaB kinase redistribution.
 - Useful for monitoring signalling pathways leading to NFkappaB activation, e.g. to identify compounds which modulate the activity of the pathway in living cells.
 - IkappaB kinase, a serine/threonine kinase, is a component of a signalling pathway which is activated by a variety of inducers including cytokines, lymphokines, growth factors and stress.
 - a) The alpha subunit of the human IkappaB kinase gene (GenBank Accession number: AF009225) is amplified using PCR according to standard protocols with primers IKK-top (SEQ ID NO:96) and IKK-bottom/+stop (SEQ ID NO:98). The PCR product is digested with restriction enzymes EcoR1 and Acc65I, and ligated into pEGFP-C1 (Clontech, Palo Alto;

GenBank Accession number U55763) digested with EcoR1and Acc65I. This produces an EGFP-IkappaB-kinase fusion (SEQ ID NO:120 &121) under the control of a CMV promoter.

b) The alpha subunit of the human IkappaB kinase gene (GenBank Accession number: AF009225) is amplified using PCR according to standard protocols with primers IKK-top (SEQ ID NO:96) and IKK-bottom/-stop (SEQ ID NO:97). The PCR product is digested with restriction enzymes EcoR1 and Acc651, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with EcoR1 and Acc651. This produces an IkappaB-kinase-EGFP fusion (SEQ ID NO:122 &123) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. Jurkat, in which the

EGFP-lkappaB-kinase probe and/or the lkappaB-kinase-EGFP probe should achieve a more
cytoplasmic distribution within seconds following stimulation with e.g. TNFalpha.

Example 12:

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Probes for detection of CDK2 redistribution.

- Useful for monitoring signalling pathways of the cell cycle, e.g. to identify compounds which modulate the activity of the pathway in living cells.
 - CDK2, a cyclin-dependent serine/threonine kinase, is a component of the signalling system which regulates the cell cycle.
- a) The human CDK2 gene (GenBank Accession number: X61622) is amplified using PCR according to standard protocols with primers CDK2-top (SEQ ID NO:102) and CDK2-bottom/+stop (SEQ ID NO: 104). The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produces an EGFP-CDK2 fusion (SEQ ID NO:114 &115) under the control of a CMV promoter.
 - b) The human CDK2 gene (GenBank Accession number: X61622) is amplified using PCR according to standard protocols with primers CDK2-top (SEQ ID NO:102) and CDK2-bottom/-stop (SEQ ID NO:103). The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and BamH1. This produces a CDK2-EGFP fusion (SEQ ID NO:112 &113) under the control of a CMV promoter.

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The resulting plasmids are transfected into a suitable cell line, e.g. HEK293 in which the EGFP-CDK2 probe and/or the CDK2-EGFP probe should change its cellular distribution from cytoplasmic in contact-inhibited cells, to nuclear location in response to activation with a number of growth factors, e.g. IGF.

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Example 13:

Probes for detection of Grk5 redistribution.

Useful for monitoring signalling pathways involving desensitization of G-protein coupled receptors, e.g. to identify compounds which modulate the activity of the pathway in living cells.

- Grk5, a G-protein coupled receptor kinase, is a component of signalling pathways involving membrane bound G-protein coupled receptors.
 - a) The human Grk5 gene (GenBank Accession number: L15388) is amplified using PCR according to standard protocols with primers Grk5-top (SEQ ID NO:27) and Grk5-
- bottom/+stop (SEQ ID NO:29). The PCR product is digested with restriction enzymes EcoR1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with EcoR1 and BamH1. This produces an EGFP-Grk5 fusion (SEQ ID NO:42 &43) under the control of a CMV promoter.
- b) The human Grk5 gene (GenBank Accession number: L15388) is amplified using PCR according to standard protocols with primers Grk5-top (SEQ ID NO:27) and Grk5-bottom/-stop (SEQ ID NO:28). The PCR product is digested with restriction enzymes EcoR1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with EcoR1 and BamH1. This produces a Grk5-EGFP fusion (SEQ ID NO:60 &61) under the control of a CMV promoter.
- The resulting plasmids are transfected into a suitable cell line, e.g. HEK293 expressing a rat dopamine D1A receptor, in which the EGFP-Grk5 probe and/or the Grk5-EGFP probe should change its cellular distribution from predominantly cytoplasmic to peripheral in response to activation of the signalling pathway with e.g. dopamine.

30 Example 14:

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Probes for detection of Zap70 redistribution.

Useful for monitoring signalling pathways involving the T cell receptor, e.g. to identify compounds which modulate the activity of the pathway in living cells.

Zap70, a tyrosine kinase, is a component of a signalling pathway which is active in e.g. T-cell differentiation.

- a) The human Zap70 gene (GenBank Accession number: L05148) is amplified using PCR according to standard protocols with primers Zap70-top (SEQ ID NO:105) and Zap70-bottom/+stop (SEQ ID NO:107). The PCR product is digested with restriction enzymes E-coR1 and BamH1, and ligated into pEGFP-C1 (GenBank Accession number U55763) digested with EcoR1 and BamH1. This produces an EGFP-Zap70 fusion (SEQ ID NO:108 &109) under the control of a CMV promoter.
- b) The human Zap70 gene (GenBank Accession number: L05148) is amplified using PCR according to standard protocols with primers Zap70-top (SEQ ID NO:105) and Zap70-bottom/-stop (SEQ ID NO:106). The PCR product is digested with restriction enzymes E-coR1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with EcoR1 and BamH1. This produces a Zap70-EGFP fusion (SEQ ID NO:110 &111) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. Jurkat, in which the

EGFP-Zap70 probe and/or the Zap70-EGFP probe should change its cellular distribution

from cytoplasmic to membrane-associated within seconds in response to activation of the T

cell receptor signalling pathway with e.g. antibodies to CD3epsilon.

Example 15:

25 Probes for detection of p85 redistribution.

Useful for monitoring signalling pathways involving PI-3 kinase, e.g. to identify compounds which modulate the activity of the pathway in living cells.

p85alpha is the regulatory subunit of PI3-kinase which is a component of many pathways involving membrane-bound tyrosine kinase receptors and G-protein-coupled receptors.

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- a) The human p85alpha gene (GenBank Accession number: M61906) was amplified using PCR according to standard protocols with primers p85-top-C (SEQ ID NO:22) and p85-bottom/+stop (SEQ ID NO:23). The PCR product was digested with restriction enzymes BgI2 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with BgI2 and BamH1. This produced an EGFP-p85alpha fusion (SEQ ID NO:48 &49) under the control of a CMV promoter.
- b) The human p85alpha gene (GenBank Accession number: M61906) was amplified using PCR according to standard protocols with primers p85-top-N (SEQ ID NO:20) and p85-bottom/-stop (SEQ ID NO:21). The PCR product was digested with restriction enzymes E-coR1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with EcoR1 and BamH1. This produced a p85alpha-EGFP fusion (SEQ ID NO:66 &67) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. CHO expressing the human insulin receptor, in which the EGFP-p85 probe and/or the p85-EGFP probe may change its cellular distribution from cytoplasmic to membrane-associated within minutes in response to activation of the receptor with insulin.

Example 16:

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Probes for detection of protein-tyrosine phosphatase redistribution.

- 20 Useful for monitoring signalling pathways involving tyrosine kinases, e.g. to identify compounds which modulate the activity of the pathway in living cells.
 - Protein-tyrosine phosphatase1C, a tyrosine-specific phosphatase, is an inhibitory component in signalling pathways involving e.g. some growth factors.
- a) The human protein-tyrosine phosphatase 1C gene (GenBank Accession number: X62055) is amplified using PCR according to standard protocols with primers PTP-top (SEQ ID NO:99) and PTP-bottom/+stop (SEQ ID NO:101). The PCR product is digested with restriction enzymes Xho1 and EcoR1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and EcoR1. This produces an EGFP-PTP fusion (SEQ ID NO:116 &117) under the control of a CMV promoter.

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b) The human protein-tyrosine phosphatase 1C gene (GenBank Accession number: X62055) is amplified using PCR according to standard protocols with primers PTP-top (SEQ ID NO:99) and PTP-bottom/-stop (SEQ ID NO:100). The PCR product is digested with restriction enzymes Xho1 and EcoR1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and EcoR1. This produces a PTP-EGFP fusion (SEQ ID NO:118 &119) under the control of a CMV promoter.

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The resulting plasmids are transfected into a suitable cell line, e.g. MCF-7 in which the EGFP-PTP probe and/or the PTP-EGFP probe should change its cellular distribution from cytoplasm to the plasma menbrane within minutes in response to activation of the growth inhibitory signalling pathway with e.g. somatostatin.

Example 17:

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Probes for detection of Smad4 redistribution.

Useful for monitoring signalling pathways involving most members of the transforming 15 growth factor-beta family, e.g. to identify compounds which modulate the activity of the pathway in living cells.

Smad4, a signal transducer, is a common component of signalling pathways induced by various members of the TGFbeta family of cytokines.

- 20 a) The human Smad4 gene (GenBank Accession number: U44378) was amplified using PCR according to standard protocols with primers Smad4-top and Smad4-bottom/+stop (SEQ ID NO:35). The PCR product was digested with restriction enzymes EcoR1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with EcoR1 and BamH1. This produce an EGFP-Smad4 fusion (SEQ ID NO:52 &53) under the control of a CMV promoter. 25
 - b) The human Smad4 gene (GenBank Accession number: U44378) was amplified using PCR according to standard protocols with primers Smad4-top (SEQ ID NO:33) and Smad4bottom/-stop (SEQ ID NO:34). The PCR product was digested with restriction enzymes EcoR1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with EcoR1 and BamH1. This produced a Smad4-EGFP fusion (SEQ ID NO:76 &77) under the control of a CMV promoter.

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The resulting plasmids are transfected into a cell line, e.g. HEK293 in which the EGFP-Smad4 probe and/or the Smad4-EGFP probe should change its cellular distribution within minutes from cytoplasmic to nuclear in response to activation of the signalling pathway with e.g. TGFbeta.

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Example 18:

Probes for detection of Stat5 redistribution.

Useful for monitoring signalling pathways involving the activation of tyrosine kinases of the Jak family, e.g. to identify compounds which modulate the activity of the pathway in living cells.

Stat5, signal transducer and activator of transcription, is a component of signalling pathways which are induced by e.g. many cytokines and growth factors.

- a) The human Stat5 gene (GenBank Accession number: L41142) was amplified using PCR according to standard protocols with primers Stat5-top (SEQ ID NO:30) and Stat5-bottom/+stop (SEQ ID NO:32). The PCR product was digested with restriction enzymes Bgl2 and Acc65I, and ligated into pEGFP-C1 (Clontech; Palo Alto; GenBank Accession number U55763) digested with Bgl2 and Acc65I. This produced an EGFP-Stat5 fusion (SEQ ID NO:54 &55) under the control of a CMV promoter.
- b) The human Stat5 gene (GenBank Accession number: L41142) was amplified using PCR according to standard protocols with primers Stat5-top (SEQ ID NO:30) and Stat5-bottom/stop (SEQ ID NO:331). The PCR product was digested with restriction enzymes Bgl2 and Acc65I, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Bgl2 and Acc65I. This produced a Stat5-EGFP fusion (SEQ ID NO:78
 &79) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. MIN6 in which the EGFP-Stat5 probe and/or the Stat5-EGFP probe should change its cellular distribution from cyto-plasmic to nuclear within minutes in response to activation signalling pathway with e.g. prolactin.

Example 19:

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Probes for detection of NFAT redistribution.

Useful for monitoring signalling pathways involving activation of NFAT, e.g. to identify compounds which modulate the activity of the pathway in living cells.

5 NFAT, an activator of transcription, is a component of signalling pathways which is involved in e.g. immune responses.

- a) The human NFAT1 gene (GenBank Accession number: U43342) is amplified using PCR according to standard protocols with primers NFAT-top (SEQ ID NO:84) and NFAT-bottom/+stop (SEQ ID NO:86). The PCR product is digested with restriction enzymes Xho1 and EcoR1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and EcoR1. This produces an EGFP-NFAT fusion (SEQ ID NO:130 &131) under the control of a CMV promoter.
- b) The human NFAT gene (GenBank Accession number: U43342) is amplified using PCR according to standard protocols with primers NFAT-top (SEQ ID NO:84) and NFAT-bottom/stop (SEQ ID NO:85). The PCR product is digested with restriction enzymes Xho1 and E-coR1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and EcoR1. This produces an NFAT-EGFP fusion (SEQ ID NO:132 &133) under the control of a CMV promoter.
- The resulting plasmids are transfected into a suitable cell line, e.g. Jurkat, in which the EGFP-NFAT probe and/or the NFAT-EGFP probe should change its cellular distribution from cytoplasmic to nuclear within minutes in response to activation of the signalling pathway with e.g. antibodies to CD3epsilon.

25 Example 20:

Probes for detection of NFkappaB redistribution.

Useful for monitoring signalling pathways leading to activation of NFkappaB, e.g. to identify compounds which modulate the activity of the pathway in living cells.

NFkappaB, an activator of transcription, is a component of signalling pathways which are responsive to a varity of inducers including cytokines, lymphokines, some immunosuppressive agents.

a) The human NFkappaB p65 subunit gene (GenBank Accession number: M62399) is amplified using PCR according to standard protocols with primers NFkappaB-top (SEQ ID NO:87) and NFkappaB-bottom/+stop (SEQ ID NO:89). The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produces an EGFP-NFkappaB fusion (SEQ ID NO:142 & 143) under the control of a CMV promoter.

- b) The human NFkappaB p65 subunit gene (GenBank Accession number: M62399) is amplified using PCR according to standard protocols with primers NFkappaB-top (SEQ ID NO:87) and NFkappaB-bottom/-stop (SEQ ID NO:88). The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; Gen-
- Bank Accession number U55762) digested with Xho1 and BamH1. This produces an NFkappaB-EGFP fusion (SEQ ID NO:140 & 141) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. Jurkat, in which the EGFP-NFkappaB probe and/or the NFkappaB-EGFP probe should change its cellular distribution from cytoplasmic to nuclear in response to activation of the signalling pathway with e.g. TNFalpha.

Example 21:

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Probe for detection of RhoA redistribution.

Useful for monitoring signalling pathways involving RhoA, e.g. to identify compounds which modulate the activity of the pathway in living cells.

RhoA, a small GTPase, is a component of many signalling pathways, e.g. LPA induced cytoskeletal rearrangements.

The human RhoA gene (GenBank Accession number: L25080) was amplified using PCR according to standard protocols with primers RhoA-top (SEQ ID NO:92) and RhoA-bottom/+stop (SEQ ID NO:93). The PCR product was digested with restriction enzymes

Hind3 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Hind3and BamH1. This produced an EGFP-RhoA fusion (SEQ ID NO:126 &127) under the control of a CMV promoter.

The resulting plasmid is transfected into a suitable cell line, e.g. Swiss3T3, in which the EGFP-RhoA probe should change its cellular distribution from a reasonably homogenous to a peripheral distribution within minutes of activation of the signalling pathway with e.g. LPA. Example 22:

Probes for detection of PKB redistribution.

Useful for monitoring signalling pathways involving PKB e.g. to identify compounds which modulate the activity of the pathway in living cells.

PKB, a serine/threonine kinase, is a component in various signalling pathways, many of which are activated by growth factors.

- a) The human PKB gene (GenBank Accession number: M63167) is amplified using PCR according to standard protocols with primers PKB-top (SEQ ID NO:36) and PKB-bottom/+stop (SEQ ID NO:80). The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produces an EGFP-PKB fusion (SEQ ID NO:138 & 139) under the control of a CMV promoter.
- b) The human PKB gene (GenBank Accession number: M63167) was amplified using PCR according to standard protocols with primers PKB-top (SEQ ID NO:36) and PKB-bottom/stop (SEQ ID NO:37). The PCR product was digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and BamH1. This produced a PKB-EGFP fusion (SEQ ID NO:70 &71) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. CHO expressing the human insulin receptor, in which the EGFP-PKB probe and/or the PKB-EGFP probe cycles between cytoplasmic and membrane locations during the activation-deactivation process following addition of insulin. The transition should be apparent within minutes.

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SEQUENCE LISTING

5	(1) GENERAL INFORMATION
	(i) APPLICANT: NovoNordisk, BioImage
10	(ii) TITLE OF THE INVENTION: A Method of Detecting Cellular Translocation of Biologically Active Polypeptides Using Fluorescense Imaging
	(iii) NUMBER OF SEQUENCES: 143
15	(iv) CORRESPONDENCE ADDRESS:(A) ADDRESSEE: NovoNordisk, BioImage(B) STREET: Mørkhøjbygade 28(C) CITY: Søborg
	(D) STATE: DK
20	(E) COUNTRY: DENMARK (F) ZIP: 2860
	(v) COMPUTER READABLE FORM:
0 E	(A) MEDIUM TYPE: Diskette
25	(B) COMPUTER: IBM Compatible (C) OPERATING SYSTEM: DOS
	(D) SOFTWARE: FastSEQ for Windows Version 2.0
30	(viii) ATTORNEY/AGENT INFORMATION:
	(A) NAME: , PV&P R
	(B) REGISTRATION NUMBER:
	(C) REFERENCE/DOCKET NUMBER:
35	·•
	(2) INFORMATION FOR SEQ ID NO:1:
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.,0	(C) STRANDEDNESS: single
	(D) TOPOLOGY: linear
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59

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		PCT/DK98/00145
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(i) SEQUENCE CHARACTERISTICS:

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(A) LENGTH: 28 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single

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(D) TOPOLOGY: linear

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40	(C) STRANDEDNESS: single (D) TOPOLOGY: linear	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:	
45	GTGGATCCCA CTGCTGCACC TGTGCTA	27
	(2) INFORMATION FOR SEQ ID NO:19:	
50	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 28 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear	
55		
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:	

	GIGGATCCTC ACTGCTGCAC CTGTGCTA	28
5	(2) INFORMATION FOR SEQ ID NO:20:	
	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 40 base pairs(B) TYPE: nucleic acid	
10	(C) STRANDEDNESS: single (D) TOPOLOGY: linear	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:	
15	CGCGAATTCC GCCACCATGA GTGCTGAGGG GTACCAGTAC	40
	(2) INFORMATION FOR SEQ ID NO:21:	
20	 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 32 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 	
25		
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:	
	CGCGGATCCT GTCGCCTCTG CTGTGCATAT AC	32
30	(2) INFORMATION FOR SEQ ID NO:22:	
35	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 30 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear	
40	(vi) ORIGINAL SOURCE: (A) ORGANISM: p85-top-C	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:	
	GGGAGATCTA TGAGTGCTGA GGGGTACCAG	30
45	(2) INFORMATION FOR SEQ ID NO:23:	
50	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 34 base pairs(B) TYPE: nucleic acid	
50	(C) STRANDEDNESS: single (D) TOPOLOGY: linear	
55	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:	
	GGGCGGATCC TCATCGCCTC TGCTGTGCAT ATAC	34 62

	(2) INFORMATION FOR SEQ ID NO:24:	
5	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 33 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear	
10	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:	
	GTGAATTCGA CCATGTCGTC CATCTTGCCA TTC	33
15	(2) INFORMATION FOR SEQ ID NO:25:	
20	 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 31 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 	
25	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:	
20	GTGGTACCCA TGACATGCTT GAGCAACGCA C	31
	(2) INFORMATION FOR SEQ ID NO:26:	
30 35	(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 32 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:	
	GTGGTACCTT ATGACATGCT TGAGCAACGC AC	32
40	(2) INFORMATION FOR SEQ ID NO:27:	
45	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 31 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear	
50	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:	
	GTGAATTCGT CAATGGAGCT GGAAAACATC G	31
55	(2) INFORMATION FOR SEQ ID NO:28:	
-0	(i) SEQUENCE CHARACTERISTICS:	

WO 98/45704	
	PCT/DK98/00145

(A) LENGTH: 30 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (xi) SEQUENCE DESCRIPTION: SEQ ID NO:28: GTGGATCCCT GCTGCTTCCG GTGGAGTTCG (2) INFORMATION FOR SEQ ID NO:29: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 31 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 20 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:29: GTGGATCCCT AGCTGCTTCC GGTGGAGTTC G	30
GTGGATCCCT GCTGCTTCCG GTGGAGTTCG (2) INFORMATION FOR SEQ ID NO:29: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 31 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (xi) SEQUENCE DESCRIPTION: SEQ ID NO:29: GTGGATCCCT AGCTGCTTCC GGTGGAGTTC G	30
GTGGATCCCT GCTGCTTCCG GTGGAGTTCG (2) INFORMATION FOR SEQ ID NO:29: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 31 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (xi) SEQUENCE DESCRIPTION: SEQ ID NO:29: GTGGATCCCT AGCTGCTTCC GGTGGAGTTC G	30
(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 31 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 20 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:29: GTGGATCCCT AGCTGCTTCC GGTGGAGTTC G	30
(A) LENGTH: 31 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 20 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:29: GTGGATCCCT AGCTGCTTCC GGTGGAGTTC G	
GTGGATCCCT AGCTGCTTCC GGTGGAGTTC G	
GTGGATCCCT AGCTGCTTCC GGTGGAGTTC G	
	31
(2) INFORMATION FOR SEQ ID NO:30:	
(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 32 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear	
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30: 35 GTAGATCTAC CATGGCGGC TGGATCCAGG CC	
(2) INFORMATION FOR SEQ ID NO:31:	2
(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 31 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single	
(D) TOPOLOGY: linear	
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:	
GTGGTACCCA TGAGAGGGAG CCTCTGGCAG A	
(2) INFORMATION FOR SEQ ID NO:32:	
(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 31 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear	

65

	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:	
5	GTGGTACCTC ATGAGAGGA GCCTCTGGCA G	31
	(2) INFORMATION FOR SEQ ID NO:33:	
10	 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 33 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 	
15	(·)	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:	
	GTGAATTCAA CCATGGACAA TATGTCTATT ACG	33
20	(2) INFORMATION FOR SEQ ID NO:34:	
25	 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 31 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 	
30	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:	
	GTGGATCCCA GTCTAAAGGT TGTGGGTCTG C	31
	(2) INFORMATION FOR SEQ ID NO:35:	
35	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 32 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single	
40	(D) TOPOLOGY: linear	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:	
	GTGGATCCTC AGTCTAAAGG TTGTGGGTCT GC	32
45	(2) INFORMATION FOR SEQ ID NO:36:	
50	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 27 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear	
55	(vi) SEQUENCE DESCRIPTION, SEC. ID NO. 25	
55	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:	

66 GTCTCGAGGC ACCATGAGCG ACGTGGC 27 (2) INFORMATION FOR SEQ ID NO:37: 5 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 27 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 10 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:37: TGGGATCCGA GGCCGTGCTG CTGGCCG 15 27 (2) INFORMATION FOR SEQ ID NO:38: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 1896 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: cDNA 25 (ix) FEATURE: (A) NAME/KEY: Coding Sequence (B) LOCATION: 1...1891 (D) OTHER INFORMATION: 30 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:38: ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu 48 35 10 GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 96 40 GAG GGC GAG GGC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile 40 TGC ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC 45 Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr 192 CTG ACC TAC GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG AAG 50 Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys 70 CAG CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu 288 55 90

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			TTC Phe									336
5			GGC Gly									384
10			GAG Glu				_			_		432
15			CAC His									480
20			AAC Asn 165					_		_		528
20	 -		GAC Asp									576
25			CCC Pro									624
30			AAC Asn									672
35			GGG Gly									720
40			CGA Arg 245									768
40			GGC Gly						_	_	_	816
45			CCG Pro									864
50			CGC Arg						_	_	_	912
55			AGC Ser								_	960

	68
	GCC ATC AAG AAG ATC AGC CCC TTC GAA CAT CAG ACC TAC TGC CAG CGC Ala lle Lys Lys lle Ser Pro Phe Glu His Gln Thr Tyr Cys Gln Arg 325 330 335
	Thr Leu Arg Glu Ile Gln Ile Leu Leu Arg Phe Arg His Glu Asn Val
10	355 360 365 ATG ASP Ile Leu Arg Ala Ser Thr Leu Glu Ala Met Arg
15	375 380 1111 Asp Lett Tyr Lys Lett
20	CTG AAA AGC CAG CAG CTG AGC AAT GAC CAT ATC TGC TAC TTC CTC TAC Leu Lys Ser Gln Gln Leu Ser Asn Asp His Ile Cys Tyr Phe Leu Tyr 395 CAG ATC CTG CGG CAG CTC TAC 1200
25	CAG ATC CTG CGG GGC CTC AAG TAC ATC CAC TCC GCC AAC GTG CTC CAC Gln Ile Leu Arg Gly Leu Lys Tyr Ile His Ser Ala Asn Val Leu His 410 415 CGA GAT CTA ANG TAU
	CGA GAT CTA AAG CCC TCC AAC CTG CTC AGC AAC ACC ACC TGC GAC CTT 1296 Arg Asp Leu Lys Pro Ser Asn Leu Leu Ser Asn Thr Thr Cys Asp Leu 420 425 430
30	AAG ATT TGT GAT TTC GGC CTG GCC CGG ATT GCC GAT CCT GAG CAT GAC Lys Ile Cys Asp Phe Gly Leu Ala Arg Ile Ala Asp Pro Glu His Asp 435 440 445
35	CAC ACC GGC TTC CTG ACG GAG TAT GTG GCT ACG CGC TGG TAC CGG GCC His Thr Gly Phe Leu Thr Glu Tyr Val Ala Thr Arg Trp Tyr Arg Ala 450 450
40	CCA GAG ATC ATG CTG AAC TCC AAG GGC TAT ACC AAG TCC ATC GAC ATC Pro Glu Ile Met Leu Asn Ser Lys Gly Tyr Thr Lys Ser Ile Asp Ile 470 475 480
45	TGG TCT GTG GGC TGC ATT CTG GCT GAG ATG CTC TCT AAC CGG CCC ATC 1488 485 490 495
45	TTC CCT GGC AAG CAC TAC CTG GAT CAG CTC AAC CAC ATT CTG GGC ATC Phe Pro Gly Lys His Tyr Leu Asp Gln Leu Asn His Ile Leu Gly Ile 500 510
50	CTG GGC TCC CCA TCC CAG GAG GAC CTG AAT TGT ATC ATC AAC ATG AAG Leu Gly Ser Pro Ser Gln Glu Asp Leu Asn Cys Ile Ile Asn Met Lys 515 520 525
55	GCC CGA AAC TAC CTA CAG TCT CTG CCC TCC AAG ACC AAG GTG GCT TGG Ala Arg Asn Tyr Leu Gln Ser Leu Pro Ser Lys Thr Lys Val Ala Trp 530 535 540

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									69					
	 -				AAG Lys 550						-			1680
5					AAC Asn									1728
10	 				CTG Leu									1776
15	 				TTC Phe							 		1824
20	 				GAG Glu									1872
20	 				GCC Ala 630		CTAG							1896
25		(2)) IN	FORM	ATIO	1 FO	R SE	Q ID	NO:3	39: ·				
	(:	i) Si	EQUE	NCE (CHAR	ACTE	RIST:	ICS:						

30

- - (A) LENGTH: 631 amino acids
- (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
 - (v) FRAGMENT TYPE: internal
 - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:
- Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu 40 5 10 Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 25
 - Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile 40
- 45 Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr 55 60
 - Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys 70 Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
- 50 90 Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
 - 105 Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly 120 125
- 55 Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr 130 135 140

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	A	sn	T	r A	sn S	er F	lis A	Asn	Va:	l Ty	/r I	le	Met	: A1	a As	I as	JVS	G1	n I.	ve	Aen
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3																					
					eu L						s T	yr							r A.		
10	S	er	Lу 21	s As O	sp P	ro A	sn G	lu i	Lys 215	Ar	g A	sp	His	Met	. Va	l L	05 eu	Let	u GI	lu	Phe
					la A		ly I	le :													
					g Se																
15					n Gl 26																
20					y Pr																
					t Va																
					s Ly									Gln							
25	Th	r 1	Leu	Arg	g Gl: 34	u Il	e Gl	n I	le	Leu	Le	u A	330 Arg	Phe	Arg	Hi	s (3lu	33! Ası	5 n V	al
					arg																
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00					Glr																
					Arg																
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					Lys 420																
					Asp																
40					Phe											Trp	T				
	Pro 465	G.	lu	Ile	Met	Leu	Asr.	ı Se	r I	ys	Gly	T	yr I	hr 1	460 Lys	Ser	1	le .	Asp	IJ	.e
					Gly																
45					Lys																
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55	Arg	ме	с I	-eu	Thr	Phe 565	Asn	Pro	A	sn]	Lys	Ar 57	g I	le T	hr '	Val	Gl	u G	lu	Al	a
55	Leu	Al	a I	lis	Pro 580	Tyr	Leu	Glu	G.	ln j	Fyr 585	Ty	r As	sp P	ro '	Thr	As	p G	75 lu	Pro	>
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	Val .		Glu 595	Glu	Pro	Phe	Thr	Phe 600	Ala	Met	Glu	Leu	Asp 605	Asp	Leu	Pro	
	Lys			Leu	Lys		Leu 615		Phe	Gln	Glu	Thr 620		Arg	Phe	Gln	
5	Pro 625	Gly	Val	Leu	Glu	Ala 630	Pro										
			(2)	INF	ORMA	TION	FOF	SEÇ	DI	NO : 4	0:						
10		(i	(A) (B) (C)	QUEN LENG TYPE STRA	TH: : nu NDED	1818 clei NESS	bas c ac : si	e pa id ngle	irs								
15		•	-	OLEC EATU		TYPE	: cI	NA									
20			(B)	LOC OTH	ATIC	N: 1	1	815	equer	ice							
				EQUE													
25	ATG Met 1																48
30	GTC Val																96
35	GAG Glu																144
40	TGC Cys			GGC Gly													192
40				GGC Gly													240
45				TTC Phe													288
50				TTC Phe 100													336
55				GAG Glu												_	384

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10		-		-	GG:	1	65	- 110	Бys	, TT	еА	rg	170	As	n Il	e G	lu	Asp	Gl 17	У 5	Ser	528
15					C GC u Al 18	0	. q	.113	ıyı	GI	1:	1n 85	Asn	Thi	r Pr	o I	le	Gly 190	As	p (Gly	576
20				19				ъъ	ASII	200)	yr .	Leu	Ser	Th	r G: 20	ln 05	Ser	Ala	a. 1	Leu	624
		2	210		C CC Pr		,,,,	- Lu	215	ALG	AS	sp 1	ils	Met	220	l L∈)	eu .	Leu	Glı	1 F	he	672
25	GT(Va. 225	3 A 1 T	CC hr	GCC	GC0 Ala	C GG a Gl	1 -	TC . le '	ACT Thr	CTC	GG G1	C A	iet	GAC Asp 235	Glu	G CT	G '	TAC Tyr	AAC Lys	S	CC er 40	720
30	GG <i>I</i> Gly	A C	TC eu	AGA Arg	Ser	CG Ar 24	y •	TA A	ACC Thr	ATG Met	GC Al	a A	CG la 50	GCG Ala	GCG Ala	GC Al	G (GCG Ala	GGC Gly 255	Þ	CG ro	768
35	GAG Glu	A' M	TG et	GTC Val	CGC Arg 260		g cz y Gi	AG (GTG /al	TTC Phe	GAG As _j 26!	pν	TG (GGG Gly	CCG Pro	CG Ar	g I	AC yr 70	ACT Thr	A:	AT sn	816
40	CTC Leu	T(CG er	TAC Tyr 275	ATC	GG# Gly	A GA / G]	AA G	TY.	GCC Ala 280	TA(C G	GC 1	ATG Met	GTT Val	TG: Cy:	S	CT er	GCT Ala	T? Ty	AT /r	864
	GAT Asp	AF As 29	AT (sn)	CTC Leu	AAC Asn	AAA Lys	GT Va	- A	GA (rg \ 95	GTT Val	GCT Ala	r At	CC A	AAG Ys	AAA Lys 300	ATC	C A	GT (CCT Pro	TT Ph	TT le	912
45	GAG Glu 305	CA Hi	.C (CAG Sln	ACC Thr	TAC Tyr	TG Cy 31	. J	AG A	AGA Arg	ACC Thr	. C.	eu A	GA rg 15	GAG Glu	ATA Ile	A A	AA 1 ys :	ATC [le	CT Le 32	u	960
50	CTG Leu	CG Ar	C I	TC he	AGA Arg	CAT His 325	GA Gl	G Az u As	AC A	ATC .	ATC Ile	GG G1 33	уΙ	TC :	AAT Asn	GAC Asp	A1	le]	TC le	CG Ar	a G	1008
55	GCA Ala	CC. Pr	A A		ATT Ile 340	GAG Glu	CA(G AT	rg A et L	ys A	GAT Asp 345	GT Va	АТ. 1 Т	AT 1 yr 1	ATA Ile	GTA Val	C# G1 35	n A	AC sp	CT:	C	1056

						13				
			CTT Leu							1104
5			TAT Tyr							1152
10			AAT Asn							1200
15			ACT Thr 405							1248
20			CCA Pro							1296
20			TGG Trp							1344
25	 		TCC Ser							1392
30			AAC Asn		_					1440
35			ATC Ile 485							1488
40			ATA Ile							1536
40			AAG Lys							1584
45			GAT Asp						_	1632
50			GTT Val							1680
55			AGT Ser 565	_			_		_	1728

										7	4						
_		-		5	80	op A	ap n	eu P	FO L.	ys G 85	lu L	ys L	eu L	ys G 5	lu L 90	TC A1	TT 1776 le
5	T P	TT G he G		AG A lu T 95	CT G hr A	CT CO	GA T'	ie G	AG Co ln P:	CA G ro G	GA T	AC AG	rg Se	CT T er 05	A A		1818
10				(2)	INFO	CTAMS	ON I	FOR S	SEQ]	D N	0:41:	:					
15			(SEQUAL LEGISTE SEQUENTS OF THE	ENGTH PE: RAND	I: 60 amin EDNE	5 am o ac SS:	nino id sinc	ació ació	S: Is							
20			(v)	MOL FRAG SEQ	MENT	TYP	E: i	nter	ein nal N: S	EQ I	D NO	:41:			1		
25			l Se	r Ly	s Gl	y Gl	u Gl	u Le	u Ph	e Th	r Gl	y Va				e Leu	
																r Gly	
																Ile Thr	
30																Thr Lys	
					Phe											80 Glu	
35					Phe				Gly	90 Asr						Glu	
	Va1	. Lys	Phe 115	Glu	Gly	Asp	Thr	Leu	Val	Asn	ı Arg	Ile	Glu	110 Leu	Lys	Gly	
40								Asn	Ile							Tyr	
												Asp				Asn	
45									Arg		Asn						
40									Gln 185								
									Tyr								
50									Asp								
									Gly								
55									Ala								
			_	260	1	J-11	7 4.1	FIIE	Asp 265	val	GIÀ	Pro	Arg	Tyr 270	Thr	Asn	

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Leu Ser Tyr Ile Gly Glu Gly Ala Tyr Gly Met Val Cys Ser Ala Tyr
                 280
            275
                                   285
     Asp Asn Leu Asn Lys Val Arg Val Ala Ile Lys Lys Ile Ser Pro Phe
                          295
5
     Glu His Gln Thr Tyr Cys Gln Arg Thr Leu Arg Glu Ile Lys Ile Leu
     305 310
                                       315
     Leu Arg Phe Arg His Glu Asn Ile Ile Gly Ile Asn Asp Ile Ile Arg
                   325
                                    330
     Ala Pro Thr Ile Glu Gln Met Lys Asp Val Tyr Ile Val Gln Asp Leu
10
               340
                                 345
     Met Glu Thr Asp Leu Tyr Lys Leu Leu Lys Thr Gln His Leu Ser Asn
           355
                             360
                                              365
     Asp His Ile Cys Tyr Phe Leu Tyr Gln Ile Leu Arg Gly Leu Lys Tyr
                          375
                                           380
15
     Ile His Ser Ala Asn Val Leu His Arg Asp Leu Lys Pro Ser Asn Leu
            390
                                        395
     Leu Leu Asn Thr Thr Cys Asp Leu Lys Ile Cys Asp Phe Gly Leu Ala
             . 405
                                    410
     Arg Val Ala Asp Pro Asp His Asp His Thr Gly Phe Leu Thr Glu Tyr
20
               420
                                425
     Val Ala Thr Arg Trp Tyr Arg Ala Pro Glu Ile Met Leu Asn Ser Lys
           435 440
                                     445
     Gly Tyr Thr´Lys Ser Ile Asp Ile Trp Ser Val Gly Cys Ile Leu Ala
                         455
                                           460
25
     Glu Met Leu Ser Asn Arg Pro Ile Phe Pro Gly Lys His Tyr Leu Asp
            470 475
     Gln Leu Asn His Ile Leu Gly Ile Leu Gly Ser Pro Ser Gln Glu Asp
                                     490
     Leu Asn Cys Ile Ile Asn Leu Lys Ala Arg Asn Tyr Leu Leu Ser Leu
30
                               505
              500
                                        510
     Pro His Lys Asn Lys Val Pro Trp Asn Arg Leu Phe Pro Asn Ala Asp
                             520
                                               525
     Ser Lys Ala Leu Asp Leu Leu Asp Lys Met Leu Thr Phe Asn Pro His
       530
                535
                                          540
35
     Lys Arg Ile Glu Val Glu Gln Ala Leu Ala His Pro Tyr Leu Glu Gln
                    550
                                       555
     Tyr Tyr Asp Pro Ser Asp Glu Pro Ile Ala Glu Ala Pro Phe Lys Phe
                  565
                                   570
     Asp Met Glu Leu Asp Asp Leu Pro Lys Glu Lys Leu Lys Glu Leu Ile
40
              580
                       585
     Phe Glu Glu Thr Ala Arg Phe Gln Pro Gly Tyr Arg Ser
                              600
             (2) INFORMATION FOR SEQ ID NO:42:
45
          (i) SEQUENCE CHARACTERISTICS:
            (A) LENGTH: 2529 base pairs
            (B) TYPE: nucleic acid
            (C) STRANDEDNESS: single
50
            (D) TOPOLOGY: linear
```

- (ii) MOLECULE TYPE: cDNA
- (ix) FEATURE:
- 55 (A) NAME/KEY: Coding Sequence
 - (B) LOCATION: 1...2526

76

(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

5	1			•		5		ıu ı	Je u	PII	10	ir G	1y	Val	Va.	l Pr	0 I	1e 5	CTG	48
10				20)	-, 11	SP V	al M	.511	25	/ ні	s L	ys 1	Phe	Ser	7 Va 30	l s	er	GGC	96
15			35		2	F		4	0	сту	гу	s Le	eu 7	Chr	Leu 45	Lу	s P	he		144
20	TGC Cys	ACC Thr 50	Th:	C GG r Gl	С АА У Ьу	G Cl	G CC u Pr 55	. v .	rg al	CCC Pro	TG(Tr)	G CC P Pr	1 O	ACC Thr	CTC Leu	GT(Va	3 AC	cc	ACC Thr	192
	CTG Leu 65	ACC Thr	ТА(Туз	GG Gl	C GT y Va	G CA 1 G1 70	л су	C T	rc . ne .	AGC Ser	CGC	TA Ty 75	r P	cc ro	GAC Asp	CA(CAI Me	rG et	AAG Lys 80	240
25	CAG (Gln)	CAC His	GAC Asp	Phe	C TTO Pho 85	C AA	G TC s Se	C GC r Al	C A	ATG Met	CCC Pro	GA.	A Go	GC '	TAC Tyr	GTC Val	CA G1 95	n	GAG Glu	288
30	CGC A	ACC Thr	ATC Ile	TTC Phe 100	TTO Phe	AA Ly	G GAG S Asj	C GA P As	рο	GC Sly 105	AAC Asn	TAC Ty:	C AZ	AG A	ACC Thr	CGC Arg 110	GC Al	C a	GAG Glu	336
35	GTG A	∙ys	TTC Phe 115	GAG Glu	GGC	GA(ACC Thi	CTC Lei	u v	TG al	AAC Asn	CGC	TA S	Le G	AG lu 25	CTG Leu	AA(G (GGC Gly	384
40	ATC G Ile A 1	AC sp 30	TTC Phe	AAG Lys	GAG Glu	GAC Asp	GGC Gly 135	HSI	C A	TC le	CTG Leu	GGG Gly	CA Hi 14	s L	AG (CTG Leu	GA(; 7	TAC Tyr	432
	AAC T Asn T 145	AC yr	AAC Asn	AGC Ser	CAC His	AAC Asn 150	GTC Val	TAT	A A	TC 1	ATG Met	GCC Ala 155	GA As	CA pL	AG (ys (CAG Gln	AAG Lys	A	AC sn 60	480
45	GGC A	rc . le :	AAG Lys	GTG Val	AAC Asn 165	TTC Phe	AAG Lys	ATC	C(A)	g E	CAC His	AAC Asn	ATO	C G/ e G)	AG C	sp	GGC Gly 175	A S	GC er	528
50	GTG CA	AG (Ln I		GCC Ala 180	GAC Asp	CAC His	TAC Tyr	CAG Gln	CA Gl	n A	AC .sn	ACC Thr	CCC Pro	C AT	.e G	GC ly .	GAC Asp	G G	gc ly	576
55	CCC G1 Pro Va	rg (eu 195	CTG Leu	CCC Pro	GAC Asp	AAC Asn	CAC His 200	TA Ty	c c	TG :	AGC Ser	ACC Thr	C CA G1 20	n S	CC (GCC Ala	C'.	rg eu	624

						77						
		CCC Pro								_		672
5		GCC Ala						_				720
10		TCT Ser										768
15		GCC Ala 260										816
20		AAA Lys										864
20		AGC Ser										912
25		TTA Leu			_		_					960
30		GAA Glu							_			1008
35		GCA Ala 340								_	_	1056
40		GAA Glu	_								_	1104
40		CAA Gln										1152
45		AAG Lys				Phe						1200
50		TAC Tyr										1248
55		GAC Asp 420										1296

												78									
	GT Va	G A		AAA Lys 435		C AC	T TI	C AC	gu	AG ln 40	TAT Tyr	CG/	A GI g Va	'G C'. .1 Le	eu	GGA Gly 445	. Ly	A G	GG ly	GGC Gly	1344
5	TT Ph		GG ly 50	GAG Glu	GT(C TG l Cy	T GC s Al	C TC a Cy 45	's G	AG ln	GTT Val	CGC	G GC J Al	C AC a Th	ır (GGT Gly	AA Ly	A AT	rg et	TAT Tyr	1392
10	GC A1 46	C T(a C ₎ 5	gc /	AAG Lys	Arg	TT J Le	G GAG u Gl	и гу	GA.	AG ys	AGG Arg	ATC	AA. Ly: 47	s Ly	G 1	AGG Arg	AA Ly	A GO s Gl	€G .y	GAG Glu 480	1440
15	TC: Se:	C At	rg (et <i>l</i>	GCC Ala	CTC	AA' Ası 48!	T GAO	3 AA 1 Ly	G CI B G	AG i	ATC Ile	CTC Leu 490	Glı	3 AA ı Ly	.G (STC Val	AA(Ası	C AG n Se 49	r	CAG Gln	1488
20	TT'. Phe	r G1 ≥ Va	rg c	GTC Val	AAC Asn 500	DCC	G GCC	TA'	T G(r A]	La '	rac ryr 505	GAG Glu	ACC Thi	C AA	G G s A	AT sp	GCA Ala	a Le	G u	TGC Cys	1536
	TTC Leu	GT Va		TG eu 15	ACC Thr	ATC	ATC Met	AA:	r GG 1 Gl 52	у	GT Sly	GAC Asp	CTC	AA(s P	TC he 25	CAC His	AT	C '	TAC Tyr	1584
25	AAC Asn	Me 53		gc ly	AAC Asn	CCT Pro	Gly	Phe 535	: GI	.G G u G	AG	GAG Glu	CGG Arg	GC0 Ala 540	a L	TG eu	TTT Phe	TA:	r (GCG Ala	1632
30	GCA Ala 545	GA:	GA' uI:	TC le	CTC Leu	TGC Cys	GGC Gly 550	TTA Leu	GA.	A G u A	AC sp	CTC Leu	CAC His 555	CGT Arg	G G	AG . lu .	AAC Asn	ACC Thi	: 1	STC /al	1680
35	TAC Tyr	CG/ Arg	A GA	AT sp	CTG Leu	AAA Lys 565	CCT Pro	GAA Glu	AA	C A	ıe i	CTG Leu 570	TTA Leu	GAT Asp	' GÆ As	T.	TAT Tyr	GGC Gly 575	Н	CAC lis	1728
40	ATT Ile	AGG	AT J Il		TCA Ser 580	GAC Asp	CTG Leu	GGC Gly	TT(ı A.	CT (la V	GTG . Val	AAG Lys	ATC Ile	CC	.0 (GAG Glu 590	GGA Gly	G	AC sp	1776
	CTG Leu	ATC	CG Ar 59	э,	GGC Gly	CGG Arg	GTG Val	GGC Gly	ACT Thr 600	Va	TT C	GC Sly	TAC Tyr	ATG Met	GC Al 60	a F	cc	GAA Glu	Gʻ Va	TC al	1824
45	CTG Leu	AAC Asn 610		.C C	CAG A	AGG Arg	TAC Tyr	GGC Gly 615	CTG Leu	AG Se	C C	CC (GAC Asp	TAC Tyr 620	TG Tr	G G p G	GC ly	CTT Leu	G(gc ly	1872
50	TGC Cys 625	CTC Leu	AT Il	ст	AT (JIU.	ATG Met 630	ATC Ile	GAG Glu	GG G1	y G	ln S	CCG Ser	CCG Pro	TT(C C	GC rg	GGC Gly	CC A1 64	£g	1920
55	AAG (GAG Glu	AA(G G s V	ω <u>τ</u> τ	AAG ys 1	CGG (Arg (GAG Glu	GAG Glu	GT Va	ΙA	AC C sp A 50	GC (CGG Arg	GT(Va]	l L	eu	GAG Glu 655	AC Th	CG ir	1968

79

						79				
			TCC Ser							2016
5			ACG Thr							2064
10			GAG Glu							2112
15			GAA Glu							2160
20			TAC Tyr 725							2208
			GTC Val							2256
25			GGC Gly							2304
30			TTT Phe							2352
35			CTG Leu							2400
40			AGA Arg 805							2448
			TCC Ser							2496
45			AAC Asn				TAG			2529

- 50 (2) INFORMATION FOR SEQ ID NO:43:
 - (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 842 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single

55

(D) TOPOLOGY: linear

80

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

5	(xi	i) SEQUEN	CE DESC	RIPTIO	N: SEQ	ID NO:43	:	
	Met Val S	Ser Lys G	ly Glu	Glu Le	u Phe	Thr Gly V	al Val F	Pro Ile Leu
10								15 al Ser Gly 0
	Giu Gly G	lu Gly A	sp Ala '	Thr Tyr 40	r Gly 1	Lys Leu T	hr Leu L 45	ys Phe Ile
15	50	nr Gly Ly	/s Leu !	Pro Val 55	Pro T	[rp Pro T] 60	nr Leu V	al Thr Thr
	65 Gln His A	yr Gly Va	70	Cys Phe	Ser A	Arg Tyr Pı 75	co Asp H	is Met Lys 80
	Arg Thr I	85 le Phe Ph	e lve v	ser Ala	Met F	oro Glu G]	y Tyr V	80 al Gln Glu 95
20	Val Lys P	100 ne Glu Gl	v Asp T	br Leu	105	sn Tyr Ly	s Thr A	95 fg Ala Glu 10 eu Lys Gly
	Ile Asp Ph 130	l5 ne Lys Gl	u Asp G	120 ly Asn	Ile I	en Gly u:	e Glu Le 125	eu Lys Gly
25	130 Asn Tyr As 145	n Ser Hi	1 s Asn V	35 al Tyr	Ile M	et Ala As	s Lys Le O D Lys Cl	u Glu Tyr
	Gly Ile Ly	s Val Ası	n Phe L	ys Ile	Arg H	155 is Asn Il	e Glu As	160 D Gly Ser
30	Val Gln Le	16! u Ala As _l 180	His T	yr Gln	1' Gln As	70 sn Thr Pro	o Ile Gl	175 Y Asp Gly
	Pro Val Le 19	u Leu Pro 5	Asp As	sn His	185 Tyr Le	eu Ser Thi	19 Gln Se	0 r Ala Leu
	Ser Lys As	p Pro Asr	Glu Ly	s Arg	Asp Hi	s Met Val	205 Leu Le	u Glu Phe
35	Val Thr Ala 225	a Ala Gly	Ile Th	r Leu	Gly Me	220 t Asp Glu 235	Leu Ty	r Lys Ser
	Gly Leu Arg					n Ser Ser		
40	Asn Ile Val							
	Gly Lys Arc 275 Pro His Ile	i Ser Cla	Lys Se	r Lys 1 280	Lys Tr	p Lys Glu	Ile Leu 285	Lys Phe
45	Pro His Ile 290 Tyr Cys Ser	Leu Cvs	29.	u Asp] 5	Leu Ar	g Arg Thr 300	Ile Asp	Arg Asp
	Tyr Cys Ser 305 Gln Phe Cys	Glu Thr	310 Arg Pro	o Glv i	ero Ile	e Gly Arg	Leu Leu	Phe Arg 320
50	Asp Ser Val	325 Ala Glu	Tyr Glu	ı Val T	33(Thr Pro	Cys Tyr	Ile Gln	Phe Leu
50	Lys Gly Lys 355	340 Glu Ile	Met Thi	3 Lys T	345 Syr Leu	Thr Pro	350	Gry Gru
	355 Phe Ile Ala 370	Gln Val	Gly Glr	Asp L	eu Val	Ser Gln	365 Thr Glu	Glu Lve
55	Leu Leu Gln 385	Lys Pro	375 Cys Lys 390	; Glu L	eu Phe	380 Ser Ala 395	Cys Ala	Gln Ser

										01						
	Val	His	Glu	Tyr	Leu 405	Arg	Gly	Glu	Pro	Phe 410	His	Glu	Tyr	Leu	Asp 415	Ser
	Met	Phe	Phe	Asp 420	Arg	Phe	Leu	Gln	Trp 425	Lys	Trp	Leu	Glu	Arg 430	Gln	Pro
5	Val	Thr	Lys 435	Asn	Thr	Phe	Arg	Gln 440	Tyr	Arg	Val	Leu	Gly 445	Lys	Gly	Gly
	Phe	Gly 450	Glu	Val	Cys	Ala	Cys 455	Gln	Val	Arg	Ala	Thr 460	Gly	Lys	Met	Tyr
10	Ala 465	Cys	Lys	Arg	Leu	Glu 470	Lys	ГÀЗ	Arg	Ile	Lys 475	Lys	Arg	Lys	Gly	Glu 480
	Ser	Met	Ala	Leu	Asn 485	Glu	Lys	Gln	Ile	Leu 490	Glu	Lys	Val	Asn	Ser 495	Gln
	Phe	Val	Val	Asn 500	Leu	Ala	Tyr	Ala	Tyr 505	Glu	Thr	Lys	Asp	Ala 510	Leu	Cys
15	Leu	Val	Leu 515	Thr	Ile	Met	Asn	Gly 520	Gly	Asp	Leu	Lys	Phe 525	His	Ile	Tyr
	Asn	Met 530	Gly	Asn	Pro	Gly	Phe 535	Glu	Glu	Glu	Arg	Ala 540	Leu	Phe	Tyr	Ala
20	Ala 545	Glu	Ile	Leu	Cys	Gly 550	Leu	Glu	Asp	Leu	His 555	Arg	Glu	Asn	Thr	Val 560
	-	_	Asp		565					570		-	.	-	575	
		_	Ile	580	_		_		585		_			590	_	-
25			Arg 595	-	_		-	600		-	-		605			
		610	Asn			-	615				_	620				
30	625		Ile	_		630			_		635			_	_	640
	•		Lys		645	_				650	_	_			655	
35			Val Leu	660			-		665				-	670		_
33	-		675 Ala			-	_	680	-		_		685	-		
		690	Arg				695	_				700	_			
40	705	-	Ala			710	_			-	715					720
		_	Lys		725	_	_	_		730	_				735	
45			-	740				_	745		_	_	_	750	-	Ile
-	-		755 Glu		_			760			_		765			
		770	Pro				775					780				
50	785		Leu			790					795					800
	-		Pro		805			•	_	810					815	_
55	His	Val	Ser	820 Ser	Asn	Ser	Thr	Gly	825 Ser	Ser				830		
			835					840								

	(2) INFORMATION FOR SEQ ID NO:44:	
5	 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 1902 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 	
10	(ii) MOLECULE TYPE: cDNA (ix) FEATURE:	
15	(A) NAME/KEY: Coding Sequence (B) LOCATION: 11899 (D) OTHER INFORMATION:	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:	
20	ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu 1 5 10 15	48
25	GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 20 25 30	96
30	GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile 35 40 45	144
	TGC ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr 55 60	192
35	CTG ACC TAC GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG AAG Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys 70 75 80	240
40	CAG CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu 85 90 95	288
45	CGC ACC ATC TTC TTC AAG GAC GAC GGC AAC TAC AAG ACC CGC GCC GAG Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu 100 105 110	336
50	GTG AAG TTC GAG GGC GAC ACC CTG GTG AAC CGC ATC GAG CTG AAG GGC Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly 115	384
	ATC GAC TTC AAG GAG GAC GGC AAC ATC CTG GGG CAC AAG CTG GAG TAC Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr 130 135 140	432
55	AAC TAC AAC AGC CAC AAC GTC TAT ATC ATG GCC GAC AAG CAG AAG AAC Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn	480

	145			150			155					160	
5								ATC Ile	_		_		528
10								CCC Pro				_	576
10								ACC Thr			_		624
15								GTC Val 220					672
20								GAG Glu					720
25								AGA Arg					768
30								ACA Thr					816
								GGA Gly					864
35								AAT Asn 300		_	_		912
40								GCC Ala					960
45			Val	Met	Cys	Asn	His	AAA Lys					1008
50								GAA Glu					1056
								CTT Leu					1104
55								CTT Leu					1152

	370	375	380
5	CTG TGT GGA ATC AAG Leu Cys Gly Ile Lys 385	CAC CTT CAT TCT His Leu His Ser 390	GCT GGA ATT ATT CAT CGG GAC 1200 Ala Gly Ile Ile His Arg Asp 395 400
10	405	Tie vai vai Lys	TCT GAT TGC ACT TTG AAG ATT Ser Asp Cys Thr Leu Lys Ile 410 415
	CTT GAC TTC GGT CTG Leu Asp Phe Gly Leu 420	GCC AGG ACT GCA Ala Arg Thr Ala 425	GGA ACG AGT TTT ATG ATG ACG 1296 Gly Thr Ser Phe Met Met Thr 430
15	CCT TAT GTA GTG ACT Pro Tyr Val Val Thr 435	CGC TAC TAC AGA Arg Tyr Tyr Arg 440	GCA CCC GAG GTC ATC CTT GGC 1344 Ala Pro Glu Val Ile Leu Gly 445
20	ATG GGC TAC AAG GAA Met Gly Tyr Lys Glu 450	AAC GTG GAT TTA Asn Val Asp Leu 455	IGG TCT GTG GGG TGC ATT ATG 1392 Frp Ser Val Gly Cys Ile Met 460
25	465	470	Phe Pro Gly Arg Asp Tyr Ile 475 480
30	485	4	TTT GGA ACA CCA TGT CCT GAA 1488 Leu Gly Thr Pro Cys Pro Glu 90 495
	TTC ATG AAG AAA CTG (Phe Met Lys Lys Leu (500	CAA CCA ACA GTA A Gln Pro Thr Val A 505	GG ACT TAC GTT GAA AAC AGA 1536 rg Thr Tyr Val Glu Asn Arg 510
35	CCT AAA TAT GCT GGA 1 Pro Lys Tyr Ala Gly 1 515	FAT AGC TTT GAG A Fyr Ser Phe Glu L 520	AA CTC TTC CCT GAT GTC CTT 1584 ys Leu Phe Pro Asp Val Leu 525
40	TTC CCA GCT GAC TCA C Phe Pro Ala Asp Ser C 530	GAA CAC AAC AAA C Glu His Asn Lys L 535	PT AAA GCC AGT CAG GCA AGG 1632 eu Lys Ala Ser Gln Ala Arg 540
45	545	50	AT GCA TCT AAA AGG ATC TCT 1680 SP Ala Ser Lys Arg Ile Ser 555 560
50	565	in his Pro Tyr I]	575
	580	585	C CCT GAC AAG CAG TTA GAT 1776 e Pro Asp Lys Gln Leu Asp 590
55	GAA AGG GAA CAC ACA AG Glu Arg Glu His Thr II	FA GAA GAG TGG AA le Glu Glu Trp Ly	A GAA TTG ATA TAT AAG GAA 1824 s Glu Leu Ile Tyr Lys Glu

85

600 595 GTT ATG GAC TTG GAG GAG AGA ACC AAG AAT GGA GTT ATA CGG GGG CAG 1872 Val Met Asp Leu Glu Glu Arg Thr Lys Asn Gly Val Ile Arg Gly Gln 5 615 620 CCC TCT CCT TTA GCA CAG GTG CAG CAG TGA 1902 Pro Ser Pro Leu Ala Gln Val Gln Gln 630 10 (2) INFORMATION FOR SEQ ID NO:45: (i) SEQUENCE CHARACTERISTICS: 15 (A) LENGTH: 633 amino acids (B) TYPE: amino acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 20 (ii) MOLECULE TYPE: protein (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:45: 25 Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu 10 Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 20 25 Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile 30 40 Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys 70 Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu 35 85 Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu 105 Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly 40 120 Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr 135 Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn 155 45 Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser 165 170 Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly 185 190 Pro Val Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu 50 195 200 205 Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe 215 220 Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser 230 235 55 Gly Leu Arg Ser Arg Ala Arg Ala Ile Met Ser Arg Ser Lys Arg Asp

85

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Asn Asn Phe Tyr Ser Val Glu Ile Gly Asp Ser Thr Phe Thr Val Leu
                   260
                        265
        Lys Arg Tyr Gln Asn Leu Lys Pro Ile Gly Ser Gly Ala Gln Gly Ile
                         280
   5
       Val Cys Ala Ala Tyr Asp Ala Ile Leu Glu Arg Asn Val Ala Ile Lys
                             295
       Lys Leu Ser Arg Pro Phe Gln Asn Gln Thr His Ala Lys Arg Ala Tyr
                         310
                                             315
       Arg Glu Leu Val Leu Met Lys Cys Val Asn His Lys Asn Ile Ile Gly
  10
                      325
                                         330
       Leu Leu Asn Val Phe Thr Pro Gln Lys Ser Leu Glu Glu Phe Gln Asp
                340
                                     345
       Val Tyr Ile Val Met Glu Leu Met Asp Ala Asn Leu Cys Gln Val Ile
                                 360
       Gln Met Glu Leu Asp His Glu Arg Met Ser Tyr Leu Leu Tyr Gln Met
  15
                             375
       Leu Cys Gly Ile Lys His Leu His Ser Ala Gly Ile Ile His Arg Asp
                                                380
                         390
                                            395
       Leu Lys Pro Ser Asn Ile Val Val Lys Ser Asp Cys Thr Leu Lys Ile
 20
                      405
                                         410
       Leu Asp Phe Gly Leu Ala Arg Thr Ala Gly Thr Ser Phe Met Met Thr
                  420
                                     425
       Pro Tyr Val Val Thr Arg Tyr Tyr Arg Ala Pro Glu Val Ile Leu Gly
                                                        430
                                440
 25
      Met Gly Tyr Lys Glu Asn Val Asp Leu Trp Ser Val Gly Cys Ile Met
                                                 445
                             455
      Gly Glu Met Val Cys His Lys Ile Leu Phe Pro Gly Arg Asp Tyr Ile
                                      460
                         470
                                           475
      Asp Gln Trp Asn Lys Val Ile Glu Gln Leu Gly Thr Pro Cys Pro Glu
 30
                                        490
      Phe Met Lys Lys Leu Gln Pro Thr Val Arg Thr Tyr Val Glu Asn Arg
                 500
                                   505
      Pro Lys Tyr Ala Gly Tyr Ser Phe Glu Lys Leu Phe Pro Asp Val Leu
                                520
      Phe Pro Ala Asp Ser Glu His Asn Lys Leu Lys Ala Ser Gln Ala Arg
                                           525
35
                   535
      Asp Leu Leu Ser Lys Met Leu Val Ile Asp Ala Ser Lys Arg Ile Ser
                        550
                                            555
      Val Asp Glu Ala Leu Gln His Pro Tyr Ile Asn Val Trp Tyr Asp Pro
40
                     565
                                       570
      Ser Glu Ala Glu Ala Pro Pro Pro Lys Ile Pro Asp Lys Gln Leu Asp
                580
                                    585
     Glu Arg Glu His Thr Ile Glu Glu Trp Lys Glu Leu Ile Tyr Lys Glu
                               600
     Val Met Asp Leu Glu Glu Arg Thr Lys Asn Gly Val Ile Arg Gly Gln
45
                           615
     Pro Ser Pro Leu Ala Gln Val Gln Gln
50
              (2) INFORMATION FOR SEQ ID NO:46:
           (i) SEQUENCE CHARACTERISTICS:
```

- (A) LENGTH: 1824 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

87

(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:

5 (A) NAME/KEY: Coding Sequence

(B) LOCATION: 1...1821
(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEC ID NO.46

10		()	(i) S	SEQUI	ENCE	DESC	RIPT	CION	SEC	Q ID	NO:4	16:					
10	ATG	GTG	AGC	AAG	GGC	GAG	GAG	CTG	TTC	ACC	GGG	GTG	GTG	ccc	ATC	CTG	48
				Lys													
	1				5					10					15		
15	פיזירי	GAG	CTG	GAC	GGC	GAC	СТА	מממ	GGC	ראר	AAG	ተ ሞር	AGC	GTG	TCC	GGC	96
,,				Asp													,,,
				20					25		_			30			
	CAC	CCC	CAC	ccc	C N TT	ccc	7.00	ma c	ccc	770	ama	x cc	cma	7 7 C	mm/c	አምሮ	344
20				GGC Gly													144
		1	35	1				40	1	-,-			45	-1-			
				GGC Gly													192
25	Cys	50	1111	Gry	шуз	ыси	55	vai	FIO	11p	FLO	60	ьец	vai	1111	1111	
				GGC													240
	65	Inr	туг	Gly	vai	70	Cys	Pne	ser	Arg	1yr 75	Pro	Asp	HIS	Met	ьув 80	
30						. •											
				TTC													288
	Gln	His	Asp	Phe	Phe 85	Lys	Ser	Ala	Met	Pro 90	Glu	Gly	Tyr	Val	Gln 95	Glu	
					0.5					90					33		
35	CGC	ACC	ATC	TTC	TTC	AAG	GAC	GAC	GGC	AAC	TAC	AAG	ACC	CGC	GCC	GAG	336
	Arg	Thr	Ile	Phe	Phe	Lys	Asp	Asp	-	Asn	Tyr	Lys	Thr	_	Ala	Glu	
				100					105					110			
	GTG	AAG	TTC	GAG	GGC	GAC	ACC	CTG	GTG	AAC	CGC	ATC	GAG	CTG	AAG	GGC	384
40	Val	гуs		Glu	Gly	Asp	Thr		Val	Asn	Arg	Ile		Leu	Lys	Gly	
			115					120					125				
	ATC	GAC	TTC	AAG	GAG	GAC	GGC	AAC	ATC	CTG	GGG	CAC	AAG	CTG	GAG	TAC	432
	Ile	_	Phe	Lys	Glu	Asp	-	Asn	Ile	Leu	Gly		Lys	Leu	Glu	Tyr	
45		130					135					140					
	AAC	TAC	AAC	AGC	CAC	AAC	GTC	TAT	ATC	ATG	GCC	GAC	AAG	CAG	AAG	AAC	480
				Ser													
50	145					150					155					160	
50	GGC	ATC	AAG	GTG	AAC	TTC	DAG	ΔΤС	CGC	CAC	AAC	ΔΤС	GAG	GAC	GGC	AGC	528
				Val													320
	-				165		•			170				=	175		
55	GTG	CAG	כיייכ	GCC	GAC	CAC	TAC	CAC	CAC	አስሮ	ACC.	ccc	ልሞሮ	ccc	GAC	GGC	576
30				Ala													3,0
					•		-							-	-	-	

	88	
	180 185 190	
5	CCC GTG CTG CCC GAC AAC CAC TAC CTG AGC ACC CAG TCC GCC CTG Pro Val Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu 195 200 205	624
10	AGC AAA GAC CCC AAC GAG AAG CGC GAT CAC ATG GTC CTG GAG TTC Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe 210 215 220	672
	GTG ACC GCC GCC GGG ATC ACT CTC GGC ATG GAC GAG CTG TAC AAG TCC Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser 230 235 240	720
15	GGA CTC AGA TCT CGA GGG AAA ATG TCT CAG GAG AGG CCC ACG TTC TAC Gly Leu Arg Ser Arg Gly Lys Met Ser Gln Glu Arg Pro Thr Phe Tyr 245 250 255	768
20	CGG CAG GAG CTG AAC AAG ACA ATC TGG GAG GTG CCC GAG CGT TAC CAG Arg Gln Glu Leu Asn Lys Thr Ile Trp Glu Val Pro Glu Arg Tyr Gln 260 265 270	816
25	AAC CTG TCT CCA GTG GGC TCT GGC GCC TAT GGC TCT GTG TGT GCT GCT Asn Leu Ser Pro Val Gly Ser Gly Ala Tyr Gly Ser Val Cys Ala Ala 275 280 285	864
30	TTT GAC ACA AAA ACG GGG TTA CGT GTG GCA GTG AAG AAG CTC TCC AGA Phe Asp Thr Lys Thr Gly Leu Arg Val Ala Val Lys Lys Leu Ser Arg 290 295 300	912
	CCA TTT CAG TCC ATC ATT CAT GCG AAA AGA ACC TAC AGA GAA CTG CGG Pro Phe Gln Ser Ile Ile His Ala Lys Arg Thr Tyr Arg Glu Leu Arg 305 310 315 320	960
35	TTA CTT AAA CAT ATG AAA CAT GAA AAT GTG ATT GGT CTG TTG GAC GTT Leu Leu Lys His Met Lys His Glu Asn Val Ile Gly Leu Leu Asp Val 325 330 335	1008
40	TTT ACA CCT GCA AGG TCT CTG GAG GAA TTC AAT GAT GTG TAT CTG GTG Phe Thr Pro Ala Arg Ser Leu Glu Glu Phe Asn Asp Val Tyr Leu Val 340 345 350	1056
45	ACC CAT CTC ATG GGG GCA GAT CTG AAC AAC ATT GTG AAA TGT CAG AAG Thr His Leu Met Gly Ala Asp Leu Asn Asn Ile Val Lys Cys Gln Lys 355 360 365	1104
50	CTT ACA GAT GAC CAT GTT CAG TTC CTT ATC TAC CAA ATT CTC CGA GGT Leu Thr Asp Asp His Val Gln Phe Leu Ile Tyr Gln Ile Leu Arg Gly 370 375 380	1152
	CTA AAG TAT ATA CAT TCA GCT GAC ATA ATT CAC AGG GAC CTA AAA CCT Leu Lys Tyr Ile His Ser Ala Asp Ile Ile His Arg Asp Leu Lys Pro 385 390 395 400	1200
55	AGT AAT CTA GCT GTG AAT GAA GAC TGT GAG CTG AAG ATT CTG GAT TTT Ser Asn Leu Ala Val Asn Glu Asp Cys Glu Leu Lys Ile Leu Asp Phe	1248

PCT/DK98/00145 WO 98/45704

89

			405			410			415		
5						ATG Met					1296
10						CTG Leu					1344
						TGC Cys					1392
15						GAC Asp					1440
20						GGG Gly 490					1488
25						ATT Ile					1536
30						ATT Ile					1584
30						TTG Leu					1632
35						TAC Tyr					1680
40						TAT Tyr 570					1728
45						AGC Ser				_	1776
						CAA Gln				TGA	1824
50											

(2) INFORMATION FOR SEQ ID NO:47:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 607 amino acids
 (B) TYPE: amino acid

90

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(C) STRANDEDNESS: single
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(D) TOPOLOGY: linear

5

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

10																					Leu
						у Аз												ı Ly	s P		
15						у Г										ır 1	Let				
						y Va									r Pi	:o 2					
20						e Ph 85								Gli							
						e Ph 0							Asn								
0.5						u Gl													ı Ly		
25						s Gl										s L	ys				
						c Hi									As	рL					
30						169								Asn	110						
												n. j	Asn								
25						Pro												Ser	Ala		
35						Asr										. Le	eu				
						Gly									Glu	Le					
40						Arg 245							3ln	Glu							
	Arg	G.	n	GIu -	Leu 260	Asn	Lys	T	hr :	Ile	Trp 265	• •	Slu	Val	Pro	G1	.u	Arg 270	Tyr	G	ln
45	Abn	T-E	u :	275	Pro	Val	Gly	S S	er (31y 280	Ala	T	yr (Gly	Ser	Va 28	1	Cys	Ala	A	la
70	PHE Dwo	29	0	ınr	гуs	Thr	Gly	29	eu <i>I</i> 95	۱rg	Val	A	la '	Val	Lys 300	Ьy	s	Leu	Ser	A	rg
	305	FII		in	ser	Ile	Ile 310	Hi	is <i>I</i>	lla	Lys	A	rg :	Thr 315	Tyr	Ar	g (3lu	Leu	A:	rg 20
50	Leu																				
	Phe																				
55	Thr	ml:	s 1 3	eu	Met	Gly	Ala	As	р L 3	eu . 60	Asn	A	sn 1	le	Val	Ly:	s C	:ys	Gln	L	/s
30	Leu	1n:	D A	sp /	Asp	His	Val	G1 37	n p	he :	Leu	I.	le T	yr (Gln 380	Ile	∍ L	eu ,	Arg	G]	Ŋ

										91							
		Lys	Tyr	Ile	His		Ala	Asp	Ile	Ile		Arg	Asp	Leu	Lys		
	385 Ser	Asn	Leu	Ala	Val	390 Asn	Glu	Asp	Cys	Glu	395 Leu	Lys	Ile	Leu	Asp	400 Phe	
5	Gly	Leu	Ala	Arg	405 His	Thr	Asp	Asp	Glu	410 Met	Thr	Gly	Tyr	Val	415 Ala	Thr	
	Ara	Trp	Tvr	420 Arg	Ala	Pro	Glu	Ile	425 Met	Leu	Asn	Trp	Met	430 His	Tvr	Asn	
	_	-	435					440				_	445		_		
10	Gin	Thr 450	Val	Asp	Ile	Trp	Ser 455	Val	GIY	Cys	He	Met 460	Ala	GIu	Leu	Leu	
	Thr 465	Gly	Arg	Thr	Leu	Phe 470	Pro	Gly	Thr	qaA	His	Ile	Asp	Gln	Leu	Lys 480	
		Ile	Leu	Arg	Leu		Gly	Thr	Pro	Gly		Glu	Leu	Leu	Lys		
15	Tle	Ser	Ser	Glu	485 Ser	Ala	Ara	Asn	Tvr	490 Tle	Gln	Ser	Leu	Thr	495 Gln	Met	
,,				500					505					510			
			515		Phe			520					525				
20	Val	Asp 530	Leu	Leu	Glu	Lys	Met 535	Leu	Val	Leu	Asp	Ser 540	Asp	Lys	Arg	Ile	
		Ala	Ala	Gln	Ala		Ala	His	Ala	Tyr		Ala	Gln	Tyr	His	-	
	545 Pro	Asp	Asp	Glu	Pro 565	550 Val	Ala	Asp	Pro	Tyr 570	555 Asp	Gln	Ser	Phe	Glu 575	560 Ser	
25	Arg	Asp	Leu		Ile	Asp	Glu	Trp	-	-	Leu	Thr	Tyr	-		Val	
	Ile	Ser	Phe	580 Val	Pro	Pro	Pro	Leu	585 Asp	Gln	Glu	Glu	Met	590 Glu	Ser		
			595					600					605				
30			(2)	IN	FORM	OITA	1 FOI	R SE) ID	NO:4	18:						
		()	i) SI	EQUE	NCE (CHARA	ACTE	RIST	ICS:								
					GTH: E: nu				airs							`	
35			(C)	STR	ANDEI	NESS	S: 8:	ingle	<u> </u>								
			(D)	TOP	DLOG	(: l:	near	r									
			ii) N ix) I		CULE	TYPE	E: cI	AMC									
40		•						_									
					ME/KE CATIO				equer	ıce							
			(D)	OTI	HER I	NFOI	TAMS:	ON:									
45		(2	(i) S	EQUI	ENCE	DESC	CRIP	rion	: SE(Q ID	NO : 4	18:					
					GGC												48
	Met 1	Val	Ser	Lys	Gly 5	Glu	Glu	Leu	Phe	Thr 10	Gly	Val	Val	Pro	Ile 15	Leu	
50	ama	C2.C	cmc	CAC	ccc	CAC	CTA	7 7 C	ccc	C A C	220	mmc	אממ	CTTC	TOO	ccc	96
					GGC Gly												30
				20					25					30			
55					GAT												144
	Glu	GTÀ	Glu	GTA	Asp	АТА	ınr	туг	GTÀ	ràs	ьeu	Inr	ьeu	гÀ2	rne	тте	

				35					4	0						45					
	T(C)	SC A	ACC Thr	AC(C GG	C AA	G CI	G CC	CC G	TG	CCC	TG	G CC	C A	20		GT	G A	CC	ACC	192
5			-					u Pr 55	,					6)						
10	Le 65	u T	hr	Ту	GG G1	y Va	G CA 1 G1 70	G TG n Cy	C T	TC he	AGC Ser	Arg	TA Ty 75	C CC	CC (GAC Asp	CA(C Al	rg et	AAG Lys 80	240
	CA Gl	G C	AC is	GAC Asp	TTO Pho	C TT Ph 85	C AA e Ly	G TC s Se	C GC	CC . la i	ATG Met	CCC Pro 90	GA Gl	A GO u Gl	C T	TAC Tyr	GT(Va]	C CA G1 95	n	GAG Glu	288
15	CG Ar	CA	CC hr	ATC Ile	Phe 100	- 111	C AA	G GA s As	C GA P As	sp (GGC Gly 105	AAC Asn	TAC Ty:	C AA r Ly	A D. I a	CC hr	CGC Arg	Al	C a	GAG Glu	336
20	GT(G A	, –	TTC Phe 115	GAC Glu	GG(C GAO	C AC	C CT r Le 12	u v	GTG Val	AAC Asn	CGC Arg	C AT	e G	AG lu 25	CTG Leu	AA Ly:	G ·	GGC Gly	384
25	ATC Ile	C GA 2 As 13		TTC Phe	AAG Lys	GAC Glu	GAC Asp	GG(Gl ₃ 135	AS	C A	ATC [le	CTG Leu	GGC Gly	CA:	s L	AG ys	CTG Leu	GA(3 ! 1 !	TAC Tyr	432
30	AAC Asn 145	TA Ty	c i	AAC Asn	AGC Ser	CAC His	AAC Asn 150	GTC Val	TA'	T A	ATC :le	ATG Met	GCC Ala 155	Asp	C AZ	AG ys (CAG Gln	AAC Lys	3 <i>7</i>	AAC Asn 160	480
	GGC Gly	AT Il	C A	AAG Lys	GTG Val	AAC Asn 165	TTC Phe	Lys	ATO	C C ∋ A	rg	CAC His 170	AAC Asn	ATC Ile	G G G I	AG (GAC Asp	GGC Gly 175	2	AGC Ser	528
35	GTG Val	CA Gl:	G (CTC Leu	GCC Ala 180	GAC Asp	CAC His	TAC Tyr	CAC Glr	1 G	AG . ln . 85	AAC Asn	ACC Thr	CCC	: AT	.e (GC Gly	GAC Asp	G	GC ly	576
40	CCC Pro	GT(TG eu 95	CTG Leu	CCC Pro	GAC Asp	AAC Asn	CAC His	17	AC (CTG Leu	AGC Ser	ACC Thr	CA G1 20	n S	CC er	GCC Ala	C	TG eu	624
45	AGC Ser	AAA Lys 210		AC sp	CCC Pro	AAC Asn	GAG Glu	AAG Lys 215	CGC	G/ As	AT (CAC Iis	ATG Met	GTC Val 220	CT Le	G C u L	TG	GAG Glu	T'	TC he	672
50	GTG Val 225	ACC Thr	G A	CC (GCC Ala	GGG Gly	ATC Ile 230	ACT Thr	CTC Leu	GG G1	GC A	let .	GAC Asp 235	GAG Glu	CT	G T	AC /	AAG Lys	Se	CC er 10	720
	GGA Gly	CTC Leu	: A(GA 7		ATG Met 245	AGT Ser	GCT Ala	GAG Glu	GG G1	уТ	AC (yr (CAG Gln	TAC Tyr	AG/ Arg	A G	la 1	CTG Leu 255	ТД Ту	AT ⁄r	768
55	GAT Asp	TAT Tyr	L)	AA A	AG (GAA . Glu .	AGA Arg	GAA Glu	GAA Glu	GA As	T A p I	TT (SAC Asp	TTG Leu	CAC His	C T	rg (GT Gly	GA As	ip /C	816

						93				
		260			265			270		
5			AAT Asn							864
10՝			AGG Arg							912
.0			GAA Glu							960
15			AAA Lys 325							1008
20			GTT Val							1056
25	 		TTG Leu							1104
20	 		CCG Pro							1152
30			GAA Glu							1200
35			TTA Leu 405	_					_	1248
40			ATC Ile							1296
45			TTA Leu							1344
50			TTA Leu							1392
50			AAG Lys							1440
55			CAG Gln							1488

									94							
				48					49					49		
5	ACC T	CC A er S	GC AA er Ly 50		T CT n Le	G TT u Le	G AA u As:	T GC n Al 50	a Ar	A GT g Va	A CTO	TC:	GA Gl: 51	u Il	T TTC e Phe	1536
10	AGC C Ser P		TG CT et Le 15	T TT u Ph	C AG	A TTO	C TC	r Ala	A GCO	C AG a Se	C TCT r Ser	GAT Asp 525	Ası	r AC	T GAA r Glu	1584
	AAC C' Asn Le	TC AT eu Il	TA AA. le Ly:	A GT	Γ ATA	A GAÆ ∋ Glu 535	1 116	TTI Let	A ATO	C TC	A ACT Thr 540	Glu	TGC	AA' Ası	r GAA n Glu	1632
15	CGA CA Arg G] 545	AG CC ln Pr	T GCZ	A CCA	A GCA Ala 550	, nen	CCT Pro	CCI Pro	AAA Lys	CCA Pro	Pro	AAA Lys	CCT Pro	ACT Thr	T ACT Thr 560	1680
20	GTA GO	C AA .a As	C AAO n Asr	GGT Gly 565	MEL	AAT Asn	' AAC Asn	AAT Asn	ATG Met 570	Ser	TTA Leu	CAA Gln	AAT Asn	GCT Ala 575	Glu	1728
25	TGG TA Trp Ty	C TG	G GGA p Gly 580	чэр	ATC Ile	TCG Ser	AGG Arg	GAA Glu 585	GAA Glu	GTG Val	AAT Asn	GAA Glu	AAA Lys 590	CTT Leu	CGA Arg	1776
30	GAT AC Asp Th	59!	5	Cly	****	File	600	vai	Arg	Asp	Ala	Ser 605	Thr	Lys	Met	1824
	CAT GG' His Gl	0		1111	Deu	615	ьeu	Arg	Lys	Gly	Gly 620	Asn	Asn	Lys	Leu	1872
35	ATC AA! Ile Lys 625	A ATA	TTT Phe	CAT His	CGA Arg 630	GAT Asp	GGG Gly	AAA Lys	TAT Tyr	GGC Gly 635	TTC Phe	TCT Ser	GAC Asp	CCA Pro	TTA Leu 640	1920
40	ACC TTO	AGT Ser	TCT	GTG Val 645	GTT Val	GAA Glu	TTA Leu	ATA Ile	AAC Asn 650	CAC His	TAC (CGG / Arg /	Asn	GAA Glu 655	TCT Ser	1968
45	CTA GCT Leu Ala	CAG Gln	TAT Tyr 660	AAT Asn	CCC . Pro :	AAA ' Lys 1	Leu .	GAT Asp 665	GTG . Val :	AAA Lys	TTA (Leu I	Leu 7	TAT Tyr 570	CCA Pro	GTA Val	2016
50	TCC AAA Ser Lys	TAC Tyr 675	CAA Gln	CAG (Gln)	GAT (Asp (3111 (GTT (Val V 580	GTC /	AAA (Lys (GAA (Glu .	Asp A	AAT A Asn I	TT (GAA (Glu)	GCT Ala	2064
	GTA GGG Val Gly 690	AAA Lys	AAA '	TTA (Leu I	115 (GAA T Glu T G95	TAT /	AAC A Asn :	ACT (3ln 1	TTT C Phe G 700	AA G	AA A	AAA A	AGT Ser	2112
55	CGA GAA Arg Glu	TAT Tyr	GAT A	AGA 1 Arg I	TTA I	AT G	AA G	SAA 7	TAT A	ACC (Thr #	CGC A Arg T	CA T hr S	CC C	CAG (GAA Glu	2160

	705			710			715					720	
5		ATG Met											2208
10		 GAA Glu											2256
		AAG Lys 755											2304
15		AAT Asn							_	_			2352
20		AGA Arg								_	_		2400
25		ATT Ile									_	_	2448
30		AAG Lys											2496
00		CAA Gln 835										_	2544
35		TAT Tyr											2592
40		ACA Thr											2640
45		CGA Arg						_		_		_	2688
50		GGC Gly									_		2736
50		GTC Val 915											2784
55		TTG Leu											2832

96

935

ACC TCC CTT GTG CAG CAC AAC GAC TCC CTC AAT GTC ACA CTA GCC TAC Thr Ser Leu Val Gln His Asn Asp Ser Leu Asn Val Thr Leu Ala Tyr 2880 5 950 955

CCA GTA TAT GCA CAG CAG AGG CGA TGA Pro Val Tyr Ala Gln Gln Arg Arg 965

2907

10

15

(2) INFORMATION FOR SEQ ID NO:49:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 968 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- 20 (ii) MOLECULE TYPE: protein (v) FRAGMENT TYPE: internal

930

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

- 25 Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu 10 Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
- 25 Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile 30
- 40 Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr 55
- Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys 70
- Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu 35 Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
 - 100 105 Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
- 40 120 Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr
 - 135 140 Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn
- 150 155 Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser 45
 - 170 Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly 185
- Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu 190 50 200 205
 - Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe 215
 - Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser 230 235
- Gly Leu Arg Ser Met Ser Ala Glu Gly Tyr Gln Tyr Arg Ala Leu Tyr 55 245 250

										91						
	Asp	Tyr	Lys	Lys 260	Glu	Arg	Glu	Glu	Asp 265	Ile	Asp	Leu	His	Leu 270	Gly	Asp
	Ile	Leu	Thr 275	Val	Asn	Lys	Gly	Ser 280	Leu	Val	Ala	Leu	Gly 285	Phe	Ser	Asp
5	Gly	Gln 290	Glu	Ala	Arg	Pro	Glu 295	Glu	Ile	Gly	Trp	Leu 300	Asn	Gly	Tyr	Asn
	Glu 305	Thr	Thr	Gly	Glu	Arg 310	Gly	Asp	Phe	Pro	Gly 315	Thr	Tyr	Val	Glu	Tyr 320
10	Ile	Gly	Arg	Lys	Lys 325	Ile	Ser	Pro	Pro	Thr 330	Pro	Lys	Pro	Arg	Pro 335	Pro
	Arg	Pro	Leu	Pro 340	Val	Ala	Pro	Gly	Ser 345	Ser	Lys	Thr	Glu	Ala 350	Asp	Val
			355		Leu			360	_				365			
15		370			Pro		375					380				
	385	_	_		Glu	390				_	395					400
20					Leu 405					410					415	
				420	Ile				425					430		
05	_		435	_	Leu			440					445		-	
25		450			Leu		455					460				
	465			•	Lys	470		_			475					480
30					Gln 485 Asn	_			_	490			-		495	
				500	Phe				505					510		
35			515		Val			520					525			
		530			Pro		535					540		-		
	545				Gly	550				-	555		-			560
40					565 Asp					570					575	
				580	Gly				585					590		
45			59 5		Thr			600			_		605			
		610			His		615					620				
	625				Val	630					635					640
50	Leu	Ala	Gln	Tyr	645 Asn	Pro	Lys	Leu	Asp	650 Val	Lys	Leu	Leu	Tyr	655 Pro	Val
	Ser	Lys	Tyr	660 Gln	Gln	Asp	Gln	Val	665 Val	Lys	Glu	Asp	Asn	670 Ile	Glu	Ala
55		Gly	675		Leu		Glu	680					685			
		690					695					700				

										98							
																1 Glu 720	
E																Lys	
5																Tyr	
								760						Glr	a Arg	Ile	
10				Туг									Glu	Ile			
				Arg								Gln	Ala				
45				Asp							Lys						
15	Leu									Met	Trp						
	Val								Trp					Asn	Thr		
20													Pro				
	Glu 1 865											Asn					
	Leu 1										Leu						
25	Lys (Val							
	His (Thr								
30								Lys				Leu					
	Thr S 945					His : 950	Asn		Ser	Leu .	Asn '	940 Val	Thr	Leu			
	Pro V	al '	Tyr .		Gln (965	Gln i	Arg .	Arg			955					960	
35			(2)	INFO	ORMA'	rion	FOR	SEO	ו מד	VO - E	0 -						
		(i)		QUENC							0:						
40			(A) 1	LENGT	TH: 2	2160	base	e pai	irs								
		((C) S	TRAN TOPOL	DEDN	IESS :	sir	ngle									
45		(ii	.) мс	LECU	LE I			JA.									
45		(ix) FE	EATUR	E :												
			(B)	NAME LOCA	TION	: 1.	21	.57	uenc	e							
50			(D)	OTHE	R IN	FORM	ATIO	N:									
				QUEN													
	ATG GT Met Va 1	G A	GC A er L	AG G ys G	GC G ly G	AG G	AG C lu L	TG T	TC A	CC G	GG G	TG G	TG C	CC A	TC C	TG	4 8
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								99				
	_	_					GGC Gly 25					96
5			•				GGC Gly					144
10							CCC Pro					192
15							AGC Ser					240
20							ATG Met					288
20							GGC Gly 105					336
25							GTG Val					384
30							ATC Ile					432
35							ATC Ile					480
40		_					CGC Arg					528
40	_	_			_		CAG Gln 185					576
45							TAC Tyr					624
50							GAT Asp					672
55							GGC Gly					720

										100								
	GGA Gly	CTC Leu	AGA Arg	TCT Ser	CGA Arg 245	GCT Ala	CAA Gln	GCT Ala	TC Se:	G AA r As 25	n S	CG A er T	CC A	ATG let	TCG Ser	TC Se 25	C ATC r Ile 5	768
5	TTG Leu	CCA Pro	TTC Phe	ACG Thr 260	CCG Pro	CCA Pro	GTT Val	GTG Val	AA0 Lys 265	s Ar	A CT	rg C	TG G eu G	ly '	TGG Trp 270	AA(G AAG s Lys	816
10	TCA (GCT (Ala (GGT (Gly (275	GGG Gly	TCT Ser	GGA Gly	GGA Gly	GCA Ala 280	GT	C GG. / Gl	A GO Y Gl	SA G	Lu G	AG 1 ln 1 85	AAT Asn	GG(Gl _y	G CAG	864
15	GAA (Glu (GAA 1 Glu 1 290	AAG :	rgg ' Frp (TGT (Cys (-1u	AAA Lys 295	GCA Ala	GTG Val	AAA Lys	A AG S Se	T CT T Le	eu Va	rg A	AAG .ys	AAC Lys	CTA Leu	912
20	AAG A Lys L 305	_		_, .	3	10	ισρ (GIU	Leu	GIU	31:	s Al 5	a I]	ет	hr	Thr	Gln 320	960
	AAC T Asn C	_		3	25	.,, D V	α, .	IIIL	тте	330	Se	r Th	r Cy	s S	er	Glu 335	Ile	1008
25	TGG G	GA C ly L		GT A er T 40	CA C	CA A	AT A sn T	111	ATA Ile 345	GAT Asp	CAC Glr	TG(G GA	p Tl	CA / nr '	ACA Thr	GGC Gly	1056
30	CTT TA	AC Ac yr Se 3!	GC T er Pl	TC T	CT G	AA C. lu G.	T11 T	CC ; hr ;	AGG Arg	TCT Ser	CTT Leu	GAT Asp	GG' Gl ₃ 36!	y Ar	er (CTC Leu	CAG Gln	1104
35	GTA TO Val Se	70		· 5 –,	, 5 0.	37	75	10 1	115	Val	Ile	Туг 380	Cys	s Ar	g I	eu	Trp	1152
40	CGC TG Arg Tr 385	_			39	0	L n.	ıs r	ils (Glu	ьец 395	Lys	Ala	Il	e G	lu .	Asn 400	1200
	TGC GA	_		40	5	110	נם בי	/5 П	ys A	410	Glu	Val	Cys	Va:	1 A 4	sn 1 15	Pro	1248
45	TAC CAC	C TA	T CAG r Gl: 420		A GT g Va	T GA l Gl	G AC	II P	CA (ro (25	GTT '	TTG Leu	CCT Pro	CCA Pro	GTZ Val 430	l Le	ΓA (∋u \	STG /al	1296
50	CCC CGA	A CAG His 435	C ACC	C GA	G AT	C CT	A AC 1 Th 44	L G.	AA C lu L	CTT (Jeu 1	CCG Pro	CCT Pro	CTG Leu 445	GAT Asp	GA As	C 7	AT Yr	1344
55	ACT CAC Thr His 450	TCC Ser	C ATT	CCA Pro	A GAA	A AA(1 Asr 455	1 111	T AZ	AC T	TC C	ro .	GCA Ala 460	GGA Gly	ATT Ile	GP Gl	ıG C	CA ro	1392

							101				
									ATC Ile		1440
5					_				GAC Asp		1488
10									AAT Asn 510	_	1536
15									TGG Trp		1584
20									TTC Phe		1632
									TCA Ser		1680
25									AAT Asn		1728
30	_	_							TTA Leu 590		1776
35									GCA Ala		1824
40									CCT Pro		1872
40									AAC Asn		1920
45									TTT Phe		1968
50									TTT Phe 670		2016
55									ACT Thr		2064

										10							
E		- 6	90			D	6.	95	TA D	го Г	eu G	In T	rp L 00	eu A	sp L	AA GTA ys Val	
5	Т Ь 7	TA A eu T 05	CT C hr G	AG A' ln M	TG G	-, -,	CC CC er Pi	CT T	CA G' er Va	TG C	rg C	GC T ys S 15	CA A	GC A' er Me	rg To ≥t Se	CA TAA er	2160
10				(2)	INFOR	CTAMS	ON I	FOR S	SEQ]	ID NO	0:51:	:					
15			() () ()	SEQUAL (A) LE	ENGTH PE: RAND	I: 71 amin EDNE	9 am o ac	nino id sinc	STICS acid	S: ls							
20			(v)	MOL FRAG SEQ	MENT	TYP	E: i	nter	ein nal N: S	EQ I	D NO	:51:					
25			l Se	r Ly	s Gl	y Glı	u Gl	u Le	u Ph	e Th	r Gl	y Va				e Leu c Gly	
			y Gl													c Gly	
30	Су	5 Th:	r Th	c Gly	, Lys	. Leu	Pro	Val	l Pro	Tr	o Pro	Th:	45 Let	ı Va]	Thi	Thr	
					Phe											Lys 80 Glu	
35	Arg	Thi	: Ile	Phe	Phe	Lys	Asp	Asp	Gly	90 Asr	туг	Lys	Thr	Arg	95 Ala	Glu	
									Val	Asn					Lys	Gly	
40									Ile Ile								
									Arg	His	155 Asn						
45	Val	Gln	Leu	Ala 180	Asp	His	Tyr	Gln	Gln	Asn	Thr	Pro	Ile	Gly	175 Asp	Gly	
									Tyr Asp					Ser			
50						Ile			Gly								
					Arg				Ser								
55									Lys 265								

	Ser	Ala	Gly 275	Gly	Ser	Gly	Gly	Ala 280	Gly	Gly	Gly	Glu	Gln 285	Asn	Gly	Gln
	Glu	Glu 290	Lys	Trp	Cys	Glu	Lys 295	Ala	Val	Lys	Ser	Leu 300	Val	Lys	Lys	Leu
5	Lys 305	Lys	Thr	Gly	Arg	Leu 310	Asp	Glu	Leu	Glu	Lys 315	Ala	Ile	Thr	Thr	Gln 320
	Asn	Суз	Asn	Thr	Lys 325	Cys	Val	Thr	Ile	Pro 330	Ser	Thr	Cys	Ser	Glu 335	Ile
10	Trp	Gly	Leu	Ser 340		Pro	Asn	Thr	Ile 345		Gln	Trp	Asp	Thr 350		Gly
	Leu	Tyr	Ser 355	Phe	Ser	Glu	Gln	Thr 360		Ser	Leu	Asp	Gly 365	Arg	Leu	Gln
	Val	Ser		Arg	Lys	Gly	Leu 375		His	Val	Ile	Tyr 380	Cys	Arg	Leu	Trp
15	Arg 385	Trp	Pro	Asp	Leu	His 390	Ser	His	His	Glu	Leu 395	Lys	Ala	Ile	Glu	Asn 400
	Cys	Glu	Tyr	Ala	Phe 405	Asn	Leu	Lys	Lys	Asp	Glu	Val	Cys	Val	Asn 415	Pro
20	Tyr	His	Tyr	Gln 420	Arg	Val	Glu	Thr	Pro 425	Val	Leu	Pro	Pro	Val 430	Leu	Val
	Pro	Arg	His 435	Thr	Glu	Ile	Leu	Thr 440	Glu	Leu	Pro	Pro	Leu 445	Asp	Asp	Tyr
	Thr	His 450	Ser	Ile	Pro	Glu	Asn 455	Thr	Asn	Phe	Pro	Ala 460	Gly	Ile	Glu	Pro
25	Gln 465	Ser	Asn	Tyr	Ile	Pro 470	Glu	Thr	Pro	Pro	Pro 475	Gly	Tyr	Ile	Ser	Glu 480
	Asp	Gly	Glu	Thr	Ser 485	Asp	Gln	Gln	Leu	Asn 490	Gln	Ser	Met	Asp	Thr 495	Gly
30	Ser	Pro	Ala	Glu 500	Leu	Ser	Pro	Thr	Thr 505	Leu	Ser	Pro	Val	Asn 510	His	Ser
	Leu	Asp	Leu 515	Gln	Pro	Val	Thr	Tyr 520	Ser	Glu	Pro	Ala	Phe 525	Trp	Cys	Ser
	Ile	Ala 530	Tyr	Tyr	Glu	Leu	Asn 535	Gln	Arg	Val	Gly	Glu 540	Thr	Phe	His	Ala
35	Ser 545	Gln	Pro	Ser	Leu	Thr 550	Val	Asp	Gly	Phe	Thr 555	Asp	Pro	Ser	Asn	Ser 560
		_		_	565	_				570			_	Asn	575	
40				580					585	_	_			Leu 590		
			595					600	_			_	605	Ala		
.=		610				_	615		_	-	-	620		Pro		
45	625	_				630	_	_			635			Asn		640
					645					650			_	Phe	655	
50		-		660		_		-	665		_			Phe 670		_
	•	-	675			•	_	680					685	Thr		-
55	_	690					695	_				700		Asp	_	vaı
55	ьеи 705	inr	GTU	мес	стА	710	Pro	ser	vaı	Arg	715	ser	ser	Met	ser	

	(2) INFORMATION FOR SEQ ID NO:52:	
5	 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 2421 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 	
10	(ii) MOLECULE TYPE: cDNA (ix) FEATURE:	
15	(A) NAME/KEY: Coding Sequence (B) LOCATION: 12418 (D) OTHER INFORMATION:	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:	
20	ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu 1 5 10 15	48
25	GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 20 25 30	96
30	GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile 45	144
	TGC ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr 50 55 60	192
35	CTG ACC TAC GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG AAG Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys 70 75 80	240
40	CAG CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu 85 90 95	288
45	CGC ACC ATC TTC TTC AAG GAC GAC GGC AAC TAC AAG ACC CGC GCC GAG Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu 100 105 110	336
50	GTG AAG TTC GAG GGC GAC ACC CTG GTG AAC CGC ATC GAG CTG AAG GGC Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly 115	384
	ATC GAC TTC AAG GAG GAC GGC AAC ATC CTG GGG CAC AAG CTG GAG TAC Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr 130 140	432
55	AAC TAC AAC AGC CAC AAC GTC TAT ATC ATG GCC GAC AAG CAG AAC ASn Tyr Asn Ser His Asn Val Tyr lle Met Ala Asp Lys Gln Lys Asn	480

								100						
	145				150				155			160		
5		ATC Ile											528	1
10		CAG Gln											576	
		GTG Val											624	
15		AAA Lys 210			_								672	
20		ACC Thr											720	
25	_	CTC Leu			_	_							768	!
30		ATG Met											816	•
30	_	GTG Val	_				_						864	
35		GCA Ala 290											912	
40		GAT Asp	_										960)
45		CCT Pro											1008	1
50		GTG Val											1056	;
00		AGG Arg											1104	ŧ
55		CAG Gln											1152	: 1

	370	275	
		375 380	
5	385 390	GTA TCA CCT GGA ATT GAT CTC TC Val Ser Pro Gly Ile Asp Leu Se 395	Gly Leu 400
10	405	CCA TCA AGT ATG ATG GTG AAG GAT Pro Ser Ser Met Met Val Lys Asp 410	Glu Tyr 415
4	420	CAG CCA TCG TTG TCC ACT GAA GGA Sin Pro Ser Leu Ser Thr Glu Gly 425 430	His Ser
. 15	435	CCA CCA AGT AAT CGT GCA TCG ACA TO Pro Ser Asn Arg Ala Ser Thr 440 445	Glu Thr
20	450	TA GCC CCA TCT GAG TCT AAT GCT eu Ala Pro Ser Glu Ser Asn Ala 55 460	ACC AGC 1392 Thr Ser
25	465 470	TT CCT GTG GCT TCC ACA AGT CAG le Pro Val Ala Ser Thr Ser Gln 475	Pro Ala 480
30	485		Ala Ser 495
	500	G CAG AAT GGA TTT ACT GGT CAG n Gln Asn Gly Phe Thr Gly Gln 505 510	Pro Ala
35	515	T ACC ACC TGG ACT GGA AGT AGG A r Thr Thr Trp Thr Gly Ser Arg 5 525	Thr Ala
40	CCA TAC ACA CCT AAT TTG CC Pro Tyr Thr Pro Asn Leu Pr 530	T CAC CAC CAA AAC GGC CAT CTT C O His His Gln Asn Gly His Leu G 5	CAG CAC 1632 In His
45	545 550	CCCC GGA CAT TAC TGG CCT GTT C Pro Gly His Tyr Trp Pro Val H 555	is Asn 560
50	565		lu Tyr 75
F.F.	580	GAA ATG GAT GTT CAG GTA GGA G Glu Met Asp Val Gln Val Gly G 585 590	lu Thr
55	TTT AAG GTT CCT TCA AGC TGC Phe Lys Val Pro Ser Ser Cys	CCT ATT GTT ACT GTT GAT GGA TAPE Pro Ile Val Thr Val Asp Gly Ty	r Val
			106

107

		595			600			605		
5			GGA Gly							1872
10			GCC Ala							1920
			TGT Cys 645							1968
15			GTC Val							2016
20			GGA Gly							2064
25			GAT Asp							2112
30			CAA Gln							2160
			GGC Gly 725							2208
35			GCT Ala							2256
40	_		ATG Met							2304
45			AAA Lys							2352
50			CTC Leu							2400
			TTA Leu 805	TGA						2421

(2) INFORMATION FOR SEQ ID NO:53:

```
(i) SEQUENCE CHARACTERISTICS:
                (A) LENGTH: 806 amino acids
                (B) TYPE: amino acid
   5
                (C) STRANDEDNESS: single
                (D) TOPOLOGY: linear
              (ii) MOLECULE TYPE: protein
              (v) FRAGMENT TYPE: internal
  10
              (xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:
       Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu
       Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
 15
                                      25
       Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
                                  40
       Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr
 20
                              55
       Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys
       Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
                                          90
       Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
 25
                                      105
       Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
                                  120
       Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr
 30
                              135
      Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn
                         150
      Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser
                                             155
                                         170
      Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
35
                                     185
      Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu
                                  200
      Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe
40
                             215
      Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser
                          230
                                              235
      Gly Leu Arg Ser Arg Ala Gln Ala Ser Asn Ser Asn Ser Thr Met Asp
                      245
                                        250
      Asn Met Ser Ile Thr Asn Thr Pro Thr Ser Asn Asp Ala Cys Leu Ser
45
                 260
                                      265
      Ile Val His Ser Leu Met Cys His Arg Gln Gly Gly Glu Ser Glu Thr
                                 280
     Phe Ala Lys Arg Ala Ile Glu Ser Leu Val Lys Lys Leu Lys Glu Lys
50
                             295
     Lys Asp Glu Leu Asp Ser Leu Ile Thr Ala Ile Thr Thr Asn Gly Ala
                                                300
                         310
     His Pro Ser Lys Cys Val Thr Ile Gln Arg Thr Leu Asp Gly Arg Leu
                                            315
     Gln Val Ala Gly Arg Lys Gly Phe Pro His Val Ile Tyr Ala Arg Leu
```

										, 00						
	Trp	Arg	Trp 355	Pro	Asp	Leu	His	Lys 360	Asn	Glu	Leu	Lys	His 365	Val	Lys	Tyr
	Сув	Gln 370	Tyr	Ala	Phe	Asp	Leu 375	Lys	Cys	Asp	Ser	Val 380	Сув	Val	Asn	Pro
5	Tyr 385	His	Tyr	Glu	Arg	Val 390	Val	Ser	Pro	Gly	Ile 395	Asp	Leu	Ser	Gly	Leu 400
	Thr	Leu	Gln	Ser	Asn 405	Ala	Pro	Ser	Ser	Met 410	Met	Val	Lys	Asp	Glu 415	Tyr
10	Val	His	Asp	Phe 420	Glu	Gly	Gln	Pro	Ser 425	Leu	Ser	Thr	Glu	Gly 430	His	Ser
			435	Ile				440					445			
	Tyr	Ser 450	Thr	Pro	Ala	Leu	Leu 455	Ala	Pro	Ser	Glu	Ser 460	Asn	Ala	Thr	Ser
15	465			Phe		470					475					480
				Gly	485					490					495	
20				Pro 500					505					510		
			515	His				520					525			
25		530		Pro			535					540				
25	545			Met		550					555					560
				Phe Ile	565					570					575	
30				580 Pro					585					590		
			5 9 5	Gly			•	600					605	-	•	
35		610		Glu			615		_		•	620				
	625			Glu		630		_		_	635			-	-	640
				Ala	645					650					655	
40				660 Pro					665					670		
			675	Phe				680					685			
45		690		Ala			695					700				
	705			Pro		710					715					720
				Ala	725					730					735	
50				740 Arg					745					750		
			755	Ile				760					765			
55	Arg	770 Ala	Leu	Gln	Leu	Leu	775 Asp	Glu	Val	Leu	His	780 Thr	Met	Pro	Ile	Ala
	785					790					795					800

110

Asp Pro Gln Pro Leu Asp 805

5	(2) INFORMATION FOR SEQ ID NO:54:	
10	 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 3120 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 	
	(ii) MOLECULE TYPE: cDNA (ix) FEATURE:	
15	(A) NAME/KEY: Coding Sequence(B) LOCATION: 13117(D) OTHER INFORMATION:	
20	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:	
	ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu 1 5 10 15	48
25	GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 20 25 30	96
30	GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC Glu Glu Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile 40 45	144
35	TGC ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr 50 60	192
40	CTG ACC TAC GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG AAG Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys 70 75 80	240
	CAG CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu 85 90 95	288
45	CGC ACC ATC TTC TTC AAG GAC GAC GGC AAC TAC AAG ACC CGC GCC GAG Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu 100 105 110	336
50	GTG AAG TTC GAG GGC GAC ACC CTG GTG AAC CGC ATC GAG CTG AAG GGC Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly 115	384
55	ATC GAC TTC AAG GAG GAC GGC AAC ATC CTG GGG CAC AAG CTG GAG TAC Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr 130 135 140	432

		AGC Ser								480
5		GTG Val								528
10		GCC Ala 180								576
15		CTG Leu								624
20		CCC Pro		_						672
20		GCC Ala								720
25		TCT Ser								768
30		CTG Leu 260								816
35		CGG Arg								864
40		GAC Asp								912
40		GGC Gly								960
45		GAT Asp								1008
50		CAG Gln 340								1056
55		CAC His	_							1104

											11									
		3	70	•	-	-01	CCG Pro	37	5	у	re r	eu '	Val	Asp 380	Ala	a Me	t Se	er (3ln	1152
5	38.	5					AAC Asn 390	. G11	ıın	r Pn	ie G.	Lu (31u 395	Leu	Arg	l Fe	u Va	1 7 4	hr 00	1200
10			•			405	GAG Glu	пес	г гуу	з гу	S Le	eu G	ln	Gln	Thr	Glı	n Gl 41	и Т 5	'yr	1248
15				4	120	-7-	CAG Gln	GIU	sei	42	u Ar 5	gI	le	Gln	Ala	Glr 430	ı Ph	e A	la	1296
20			4	35			AGC Ser	FLO	440	GI	ı Ar	g L	eu	Ser	Arg 445	Glu	Th	r A	la	1344
		45	0		7-2	0111	GTG Val	455	ren	GI	ı Al	а Т:	rp 1	Leu 460	Gln	Arg	Glı	ı A]	la	1392
25	465						TAC Tyr 470	AIG	val	GIU	Let	1 A. 47	la (3lu	Lys	His	Glr	1 Ly 48	's 10	1440
30	ACC Thr	CTC	G CA	G C		CTG (Leu 1 185	CGG . Arg :	AAG Lys	CAG Gln	CAG Gln	AC0 Thr 490	: 11	CC A	TC (CTG Leu	GAT Asp	GAC Asp 495	Gl	.G u	1488
35				50	00	., .		arg	GIN	505	Leu	ı Al	a G	ly A	Asn	Gly 510	Gly	Pr	0	1536
40	CCC Pro		51	5	_		.cp (/aı	520	GIN	ser	Tr	рC	ys G 5	31u 1 525	Lys	Leu	Ala	a	1584
•	GAG Glu	ATC Ile 530	ATC Ile	Tr Tr	GC.	AG A ln A		rg (CAG Gln	CAG Gln	ATC Ile	CG	g A:	GG G rg A 10	CT (GAG Glu	CAC His	CT(2	1632
45	TGC Cys 545	CAG Gln	CAC Glr	CT Le	G Co u Pi		TC C le P 50	cc (GC Gly	CCA Pro	GTG Val	GAG Glu 555	1 G.	AG A lu M	TG (TG eu	GCC Ala	GAG Glu 560	ì	1680
50	GTC 7	AAC Asn	GCC Ala	AC Th	C A7 r I] 56		CG G hr A	AC A	le	rre	TCA Ser 570	GCC Ala	CT Le	G G	TG A al T	hr :	AGC Ser	ACA Thr	•	1728
55	TTC A	ATC [le	ATT Ile	GAG Glu 580	- 3	AG C? 's G]	AG Co	CT C	10 (CAG Sln 585	GTC Val	CTG Leu	AA Ly	.G A(nr G	AG 1 ln 1	ACC .	AAG Lys		1776

							113				
			GCC Ala 595								1824
5			CCC Pro								1872
10			CTG Leu								1920
15	_		AAC Asn		_	_				_	1968
20			GCC Ala								2016
			CGG Arg 675								2064
25		_	TCT Ser								2112
30			CTG Leu								2160
35			GCC Ala								2208
40	_		GTG Val								2256
40		_	GCG Ala 755								2304
45			ACC Thr								2352
50			AGC Ser			 		 -	-		2400
55			TTC Phe								2448

						114				
	CAG TO Gln Tr	•	SAC GGG Asp Gly	GTG ATG Val Met	GIU V	TG TTG al Leu 25	AAG AAG Lys Lys	CAC CAG His Hi:	C AAG CCC s Lys Pro	2496
5		835	op Giy	nia lie	840	ry Phe	Val Asn	Lys Glr 845	A CAG GCC n Gln Ala	2544
10	85	0	- 11c /	855	PIO A	sp Gly	Thr Phe 860	Leu Leu	G CGC TTT Arg Phe	2592
15	865		8	770 170	iie ii	ir ile	Ala Trp 875	Lys Phe	GAC TCC Asp Ser 880	2640
20			885	ip Asii	ьеи ьу	890	Phe Thr	Thr Arg	GAT TTC Asp Phe 895	2688
05		90	00	ra Asp	90 90	u Gly . 5	Asp Leu	Ser Tyr 910	CTC ATC Leu Ile	2736
25	-	915	- пор и	rg FIO	920	p Glu		Ser Lys 925	Tyr Tyr	2784
30	930		u Dj	935	val Asl	b GIA 1	FAT GTG A Fyr Val 1 940	Lys Pro	Gln Ile	2832
35	AAG CAA Lys Gln 945		95	iu Phe (/al Asr	ı Ala S	Ser Ala <i>I</i> 955	Asp Ala	Gly Gly 960	2880
40	AGC AGC Ser Ser		965	c Asp G	ın Ala	970	er Pro A	Ala Val	Cys Pro 975	2928
AE	CAG GCT Gln Ala	980	1	c lyr P	985	Asn P	ro Asp H	is Val 1 990	Leu Asp	2976
45		995		10:	oo Sp Giu	Thr M	et Asp V 10	al Ala <i>I</i> 05	Arg His	3024
50	GTG GAG (Val Glu (1010		zea mg	1015	ro met	Asp Se	er Leu A:	sp Ser A	irg Leu	3072
55	TCG CCC (Ser Pro 1 1025	CCT GCC Pro Ala	GGT CTT Gly Leu 1030	. FILE II	CC TCT ir Ser	GCC AC Ala Ar 103	g Gly Se	CC CTC Ter Leu S	CA TGA er 1	3120

(2) INFORMATION FOR SEQ ID NO:55:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 1039 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- 10 (ii) MOLECULE TYPE: protein

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser Gly Leu Arg Ser Thr Met Ala Gly Trp Ile Gln Ala Gln Gln Leu Gln Gly Asp Ala Leu Arg Gln Met Gln Val Leu Tyr Gly Gln His Phe Pro Ile Glu Val Arg His Tyr Leu Ala Gln Trp Ile Glu Ser Gln Pro Trp Asp Ala Ile Asp Leu Asp Asn Pro Gln Asp Arg Ala Gln Ala Thr Gln

Leu Leu Glu Gly Leu Val Gln Glu Leu Gln Lys Lys Ala Glu His Gln

Val Gly Glu Asp Gly Phe Leu Leu Lys Ile Lys Leu Gly His Tyr Ala

	116	
	Thr Gln Leu Gln Lys Thr Tyr Asp Arg Cys Pro Leu Glu Leu Val Arg	
	Cys Ile Arg His Ile Lev Time 3-2	i
5	Cys Ile Arg His Ile Leu Tyr Asn Glu Gln Arg Leu Val Arg Glu Ala 355 360 365	
J	370 Ala Gly Ile Leu Val Asp Ala Met Ser Gln	
	Lys His Leu Gln Ile Asn Gln Thr Phe Glu Glu Leu Arg Leu Val mbu	
	Gln Asp Thr Glu Asp Clu Leu Ly 395 400	
10	Gln Asp Thr Glu Asn Glu Leu Lys Lys Leu Gln Gln Thr Gln Glu Tyr 405 410	
	Phe Ile Ile Gln Tyr Gln Glu Ser Leu Arg Ile Gln Ala Gln Phe Ala	
	Gln Leu Ala Gln Leu Ser Pro Gln Glu Arg Leu Ser Arg Glu Thr Ala	
15	Leu Gln Gln Lys Gln Val Ser Lov Gl. 23	
	Leu Gln Gln Lys Gln Val Ser Leu Glu Ala Trp Leu Gln Arg Glu Ala 450 455 460	
	Gln Thr Leu Gln Gln Tyr Arg Val Glu Leu Ala Glu Lys His Gln Lys 465 470	
20	Thr Leu Gln Leu Leu Arg Lys Gln Gln Thr Ile Ile Leu Asp Asp Glu	
20	Leu Ile Gln Trp Lys Arg Arg Gln Gln Leu Ala Gly Asn Gly Gly Pro	
	500 505 510	
	Pro Glu Gly Ser Leu Asp Val Leu Gln Ser Trp Cys Glu Lys Leu Ala 515 520 535	
25	Glu Ile Ile Trp Gln Asn Arg Gln Gln Ile Arg Arg Ala Glu His Leu	
	Cys Gln Gln Leu Pro Ile Pro Gly Pro Val Glu Glu Met Leu Ala Glu 545 550	
	545 550 550 555 560	
30	Val Asn Ala Thr Ile Thr Asp Ile Ile Ser Ala Leu Val Thr Ser Thr 565 570	
	Fine lie lie Glu Lys Gln Pro Pro Gln Val Leu Lys Thr Gln Thr Lys	
	Phe Ala Ala Thr Val Arg Leu Leu Val Gly Gly Lys Leu Asn Val His	
35	Met Asn Pro Pro Gln Val Lyc Nlo mb 73	
	Met Asn Pro Pro Gln Val Lys Ala Thr Ile Ile Ser Glu Gln Gln Ala 610 615 620	
	Lys Ser Leu Leu Lys Asn Glu Asn Thr Arg Asn Glu Cys Ser Gly Glu	
40	Ile Leu Asn Asn Cys Cys Val Met Glu Tyr His Gln Ala Thr Gly Thr	
	Leu Ser Ala His Phe Arg Asn Met Ser Leu Lys Arg Ile Lys Arg Ala	
	ASD Arg Arg Clu Ala Cl	
AF	Asp Arg Arg Gly Ala Glu Ser Val Thr Glu Glu Lys Phe Thr Val Leu 675 680	
45	Phe Glu Ser Gln Phe Ser Val Gly Ser Asn Glu Leu Val Phe Gln Val	
	Lys Thr Leu Ser Leu Pro Val Val Val Ile Val His Gly Ser Gln Asp	
	705 710 715 720 715 720	
50	His Asn Ala Thr Ala Thr Val Leu Trp Asp Asn Ala Phe Ala Glu Pro 725 730	
	740 740 740 740 740 740 740 740 740 740	
	Cys Glu Ala Leu Asn Met Lys Phe Lys Ala Glu Val Gln Ser Asn Arg	
55	Gly Leu Thr Lys Glu Asn Leu Val Phe Leu Ala Gln Lys Leu Phe Asn 770 775	
	770 775 The Leu Ala Gln Lys Leu Phe Asn 780	

117

										117							
	Asn 785	Ser	Ser	Ser	His	Leu 790	Glu	Asp	Tyr	Ser	Gly 795	Leu	Ser	Val	Ser	Trp 800	
	Ser	Gln	Phe	Asn	Arg 805	Glu	Asn	Leu	Pro	Gly 810	Trp	Asn	Tyr	Thr	Phe 815	Trp	
5	Gln	Trp	Phe	Asp 820	Gly	Val	Met	Glu	Val 825	Leu	Lys	Lys	His	His 830	rys	Pro	
	His	Trp	Asn 835	Asp	Gly	Ala	Ile	Leu 840	Gly	Phe	Val	Asn	Lys 845	Gln	Gln	Ala	
10	His	Asp 850	Leu	Leu	Ile	Asn	Lys 855	Pro	Asp	Gly	Thr	Phe 860	Leu	Leu	Arg	Phe	
	Ser 865	Asp	Ser	Glu	Ile	Gly 870	Gly	Ile	Thr	Ile	Ala 875	Trp	Lys	Phe	Asp	Ser 880	
	Pro	Glu	Arg	Asn	Leu 885	Trp	Asn	Leu	Lys	Pro 890	Phe	Thr	Thr	Arg	Asp 895	Phe	
15	Ser	Ile	Arg	Ser 900	Leu	Ala	Asp	Arg	Leu 905	Gly	Asp	Leu	Ser	Tyr 910	Leu	Ile	
	Tyr	Val	Phe 915	Pro	Asp	Arg	Pro	Lys 920	Asp	Glu	Val	Phe	Ser 925	Lys	Tyr	Tyr	
20	Thr	Pro 930	Val	Leu	Ala	Lys	Ala 935	Val	Asp	Gly	Tyr	Val 940	Lys	Pro	Gln	Ile	
	Lys 945	Gln	Val	Val	Pro	Glu 950	Phe	Val	Asn	Ala	Ser 955	Ala	Asp	Ala	Gly	Gly 960	
	ser	Ser	Ala	Thr	Tyr 965	Met	Asp	Gln	Ala	Pro 970	Ser	Pro	Ala	Val	Cys 975	Pro	
25	Gln	Ala	Pro	Tyr 980	Asn	Met	Tyr	Pro	Gln 985	Asn	Pro	Asp	His	Val 990	Leu	Asp	
	Gln	Asp	Gly 995	Glu	Phe	qaA		Asp 1000	Glu	Thr	Met	_	Val 1005	Ala	Arg	His	
30	:	1010			Leu		1015			_		1020	_		_	Leu	
	Ser 025	Pro	Pro	Ala	Gly	Leu L030	Phe	Thr	Ser		Arg 1035	Gly	Ser	Leu		ı	
			(2)) IN	FORM	ATIOI	v FOI	R SE	Q ID	NO:	56:						
35		(:			VCE (
			(B)	TYP	GTH: E: nu	ıcle	ic a	cid									
40					ANDEI OLOG			_	9								
				MOLE	CULE	TYPI	E: cl	DNA									
45		(-	•			2V · (odi.	na Si	-aue	nce							
4.0	(A) NAME/KEY: Coding Sequence (B) LOCATION: 11872 (D) OTHER INFORMATION:																
50		(2	xi) s	SEQUI	ENCE	DES	CRIP	rion	: SE	Q ID	ио:	56:					
				_	GCG Ala												48
	1				5				1	10	1	1	1		15	J	
55					GTC Val												96

Gly Thr Ala Gly Val Val Pro Val Val Pro Gly Glu Val Glu Val Val

	118												
	20 25 30												
5	AAG GGG CAG CCA TTC GAT GTG GGC CCA CGC TAC ACG CAG CTG CAG TAC Lys Gly Gln Pro Phe Asp Val Gly Pro Arg Tyr Thr Gln Leu Gln Tyr 35 40 45	144											
10	ATC GGC GAG GGC GCG TAC GGC ATG GTC AGC TCA GCT TAT GAC CAC GTG Ile Gly Glu Gly Ala Tyr Gly Met Val Ser Ser Ala Tyr Asp His Val 50 55 60	192											
	CGC AAG ACC AGA GTG GCC ATC AAG AAG ATC AGC CCC TTT GAG CAT CAA Arg Lys Thr Arg Val Ala Ile Lys Lys Ile Ser Pro Phe Glu His Gln 65 70 75 80	240											
15	ACC TAC TGT CAG CGC ACG CTG AGG GAG ATC CAG ATC TTG CTG CGA TTC Thr Tyr Cys Gln Arg Thr Leu Arg Glu Ile Gln Ile Leu Leu Arg Phe 85 90 95	288											
20	CGC CAT GAG AAT GTT ATA GGC ATC CGA GAC ATC CTC AGA GCG CCC ACC Arg His Glu Asn Val Ile Gly Ile Arg Asp Ile Leu Arg Ala Pro Thr 100 105 110	336											
25	CTG GAA GCC ATG AGA GAT GTT TAC ATT GTT CAG GAC CTC ATG GAG ACA Leu Glu Ala Met Arg Asp Val Tyr Ile Val Gln Asp Leu Met Glu Thr 115 120 125	384											
30	GAC CTG TAC AAG CTG CTT AAA AGC CAG CAG CTG AGC AAT GAC CAC ATC Asp Leu Tyr Lys Leu Leu Lys Ser Gln Gln Leu Ser Asn Asp His Ile 130 140	432											
	TGC TAC TTC CTC TAC CAG ATC CTC CGG GGC CTC AAG TAT ATA CAC TCA Cys Tyr Phe Leu Tyr Gln Ile Leu Arg Gly Leu Lys Tyr Ile His Ser 150 155 160	480											
35	GCC AAT GTG CTG CAC CGG GAC CTG AAG CCT TCC AAT CTG CTT ATC AAC Ala Asn Val Leu His Arg Asp Leu Lys Pro Ser Asn Leu Leu Ile Asn 165 170 175	528											
40	ACC ACC TGC GAC CTT AAG ATC TGT GAT TTT GGC CTG GCC CGG ATT GCT Thr Thr Cys Asp Leu Lys Ile Cys Asp Phe Gly Leu Ala Arg Ile Ala 180 185 190	576											
45	GAC CCT GAG CAC GAC CAC ACT GGC TTT CTG ACG GAG TAT GTG GCC ACA Asp Pro Glu His Asp His Thr Gly Phe Leu Thr Glu Tyr Val Ala Thr 195 200 205	624											
50	CGC TGG TAC CGA GCC CCA GAG ATC ATG CTT AAT TCC AAG GGC TAC ACC Arg Trp Tyr Arg Ala Pro Glu Ile Met Leu Asn Ser Lys Gly Tyr Thr 210 220	672											
	AAA TCC ATC GAC ATC TGG TCT GTG GGC TGC ATT CTG GCT GAG ATG CTC Lys Ser Ile Asp Ile Trp Ser Val Gly Cys Ile Leu Ala Glu Met Leu 235 240	720											
55	TCC AAC CGG CCC ATC TTC CCC GGC AAG CAC TAC CTG GAC CAG CTC AAC Ser Asn Arg Pro Ile Phe Pro Gly Lys His Tyr Leu Asp Gln Leu Asn	768 118											

						119					
			245			250			255		
5		_	ATC Ile							816	
10			AAG Lys							864	
			TGG Trp							912	
15			GAC Asp							960	
20			GCG Ala 325							1008	
25			CCA Pro							1056	
30			CCC Pro							1104	
			CAG Gln							1152	
35			GAA Glu							1200	
40			GTT Val 405							1248	
45			ACA Thr			_		 		 1296	
50			CCT Pro							1344	
00			TGC Cys							1392	
55			AGT Ser							1440	1

	120	
	465 470 475 480	
5	ATA TTT TAC AAA GAT GAC GGG AAC TAC AAG ACA CGT GCT GAA GTC AAG Ile Phe Tyr Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu Val Lys 485 490 495	1488
10	TTT GAA GGT GAT ACC CTT GTT AAT AGA ATC GAG TTA AAA GGT ATT GAT Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly Ile Asp 500 510	1536
	TTT AAA GAA GAT GGA AAC ATT CTT GGA CAC AAA ATG GAA TAC AAT TAT Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Met Glu Tyr Asn Tyr 515 520 525	1584
15	AAC TCA CAT AAT GTA TAC ATC ATG GCA GAC AAA CCA AAG AAT GGC ATC Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Pro Lys Asn Gly Ile 530 535 540	1632
20	AAA GTT AAC TTC AAA ATT AGA CAC AAC ATT AAA GAT GGA AGC GTT CAA Lys Val Asn Phe Lys Ile Arg His Asn Ile Lys Asp Gly Ser Val Gln 545 550 555	1680
25	TTA GCA GAC CAT TAT CAA CAA AAT ACT CCA ATT GGC GAT GGC CCT GTC Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly Pro Val 565 570 575	1728
30	CTT TTA CCA GAC AAC CAT TAC CTG TCC ACG CAA TCT GCC CTT TCC AAA Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu Ser Lys 580 585 590	1776
25	GAT CCC AAC GAA AAG AGA GAT CAC ATG ATC CTT CTT GAG TTT GTA ACA Asp Pro Asn Glu Lys Arg Asp His Met Ile Leu Leu Glu Phe Val Thr 595 600 605	1824
35	GCT GCT GGG ATT ACA CAT GGC ATG GAT GAA CTA TAC AAA CCT CAG GAG T Ala Ala Gly Ile Thr His Gly Met Asp Glu Leu Tyr Lys Pro Gln Glu 610 620	1873
40	(2) INFORMATION FOR SEQ ID NO:57:	1875
45	 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 624 amino acids (B) TYPE: amino acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 	
50	(ii) MOLECULE TYPE: protein (v) FRAGMENT TYPE: internal	
55	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57: Met Ala Ala Ala Ala Ala Pro Gly Gly Gly Gly Glu Pro Arg 1 5 10 15 Gly Thr Ala Gly Val Val Pro Val Val Pro Gly Glu Val Glu Val Val	

										121						
				20					25					30		
	Lys	Gly	Gln	Pro	Phe	Asp	Val	Gly	Pro	Arg	Tyr	Thr	Gln	Leu	Gln	Tyr
			35					40		_	-		45			•
5	Ile	Gly 50	Glu	Gly	Ala	Tyr	Gly 55	Met	Val	Ser	Ser	Ala 60	Tyr	Asp	His	Val
	Arq	Lys	Thr	Arg	Val	Ala		Lvs	Lvs	Ile	Ser		Phe	Glu	His	Gln
	65	•		~		70		- 4			75					80
	Thr	Tyr	Cvs	Gln	Arg	Thr	Leu	Ara	Glu	Ile		Ile	Leu	Leu	Ara	
		•	4		85			5		90					95	
10	Arg	His	Glu	Asn	Val	Ile	Gly	Ile	Arq	Asp	Ile	Leu	Arq	Ala	Pro	Thr
	_			100			•		105	•				110		
	Leu	Glu	Ala	Met	Arg	Asp	Val	Tyr	Ile	Val	Gln	Asp	Leu	Met	Glu	Thr
			115					120				_	125			
	Asp	Leu	Tyr	Lys	Leu	Leu	Lys	Ser	Gln	Gln	Leu	Ser	Asn	Asp	His	Ile
15		130					135					140				
	Cys	Tyr	Phe	Leu	Tyr	Gln	Ile	Leu	Arg	Gly	Leu	Lys	Tyr	Ile	His	Ser
	145					150					155					160
	Ala	Asn	Val	Leu	His	Arg	Asp	Leu	Lys	Pro	Ser	Asn	Leu	Leu	Ile	Asn
					165					170					175	
20				180	Leu				185					190		
	Asp	Pro	Glu	His	Asp	His	Thr	Gly	Phe	Leu	Thr	Glu	Tyr	Val	Ala	Thr
			195					200					205			
25	Arg	Trp 210	Tyr	Arg	Ala	Pro	Glu 215	Ile	Met	Leu	Asn	Ser 220	Lys	Gly	Tyr	Thr
	Lys	Ser	Ile	Asp	Ile	Trp	Ser	Val	Gly	Суз	Ile	Leu	Ala	Glu	Met	Leu
	225					230					235					240
	Ser	Asn	Arg	Pro	Ile	Phe	Pro	Gly	Lys	His	Tyr	Leu	Asp	Gln	Leu	Asn
					245					250					255	
30	His	Ile	Leu		Ile	Leu	Gly	Ser		Ser	Gln	Glu	Asp		Asn	Cys
			_	260	_		_		265					270		
	11e	ше		Met	Lys	Ala	Arg		Tyr	Leu	Gln	Ser		Pro	Ser	Lys
	/Dla sa	*	275		m	77-	T	280	D 1		-		285			
35	Int	ьуs 290	vai	Ala	Trp	Ата		ьеп	Pne	Pro	гàз		Asp	ser	rys	АТА
33	Lou		Lou	T 011	λαν	7~~	295 Mot	7 011	mb~	Dha	n	300	7	T	7	T1.
	305	кэр	Бец	пец	Asp	310	Mec	nea	1111	Pne	315	PIO	ASII	Lys	Arg	320
		Val	Glu	Glu	Ala		ΔΊа	Hie	Dro	Tur		Glu	Gln	Tree	Tur	
					325			*****		330	пси	Gru	O111	171	335	rsp
40	Pro	Thr	qaA	Glu	Pro	Val	Ala	Glu	Glu		Phe	Thr	Phe	Asp		Glu
				340					345					350		
	Leu	Asp	Asp	Leu	Pro	Lys	Glu	Arg	Leu	Lvs	Glu	Leu	Ile		Gln	Glu
		_	355			•		360		1			365			
	Thr	Ala	Arg	Phe	Gln	Pro	Gly	Ala	Pro	Glu	Gly	Pro	Gly	Arg	Ala	Met
45		370					375				-	380	-	_		
	Ser	Lys	Gly	Glu	Glu	Leu	Phe	Thr	Gly	Val	Val	Pro	Ile	Leu	Val	Glu
	385					390					395					400
	Leu	Asp	Gly	Asp	Val	Asn	Gly	Gln	Lys	Phe	Ser	Val	Ser	Gly	Glu	Gly
_					405					410					415	
50	Glu	Gly	Asp	Ala	Thr	Tyr	Gly	Lys	Leu	Thr	Leu	Lys	Phe	Ile	Cys	Thr
				420					425					430		
	Thr	Gly		Leu	Pro	Val	Pro		Pro	Thr	Leu	Val		Thr	Leu	Thr
	m.	~ 3	435	<i>~</i> ?	_		_	440	_		_		445			•
EE	Tyr		va1	Gin	Cys	Phe		Arg	Tyr	Pro	Asp		Met	Lys	Gln	His
55	7	450	Dle -	T	0		455	_			_	460	~,			_,
	Asp	Pne	Pne	ràs	Ser	Ala	Met	Pro	Glu	Gly	Tyr	Val	Gln	Glu	Arg	Thr

	122	
	465 470 475	
	Ile Phe Tyr Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu Val Lys	
	485 490 405	
5	Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly Ile Asp	
	Phe Lys Glu Asp Cly Asp The Son The So	
	Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Met Glu Tyr Asn Tyr 515	
	Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Pro Lys Asn Gly Ile	
40	530 535 FAO Lys Asn Gly Ile	
10	Lys Val Asn Phe Lys Ile Arg His Asn Ile Lys Asp Gly Ser Val Gln 545 550	
	Leu Ala Asp His Tur Cla	
	The His Tyl Gin Gin Asn Thr Pro Ile Gly Asn Gly Pro Val	
	Leu Leu Pro Asp Asp His Thurston 570 575	
15	Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu Ser Lys	
	Asp Pro Asn Glu Lys Arg Asp His Met Ile Leu Leu Glu Phe Val Thr	
	595 600 FOR THE Lett Lett Glu Phe Val Thr	
	Ala Ala Gly Ile Thr His Gly Met Asp Glu Leu Tyr Lys Pro Gln Glu	
20	610 615 620	
	(2) INFORMATION TO	
	(2) INFORMATION FOR SEQ ID NO:58:	
	(i) SEQUENCE CHARACTERISTICS:	
0.5	(A) LENGTH: 1815 base pairs	
25	(B) TYPE: nucleic acid	
	(C) STRANDEDNESS: single	
	(D) TOPOLOGY: linear	
	(ii) MOLECULE TYPE: CDNA	
30	(ix) FEATURE:	
	(A) NAME/KEY: Coding Sequence	
	(B) LOCATION: 11811	
35	(D) OTHER INFORMATION:	
	(xi) SEQUENCE DESCRIPTION	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:	
	ATG GCG GCG GCG GCG GCG GGC CCG GAG ATG GTC CGC GGG CAG GTG Met Ala Ala Ala Ala Ala Ala Gly Bro Cly Met Ala Ala Ala Ala Ala Gly Bro Cly Met Ala Ala Ala Ala Ala Ala Ala Gly Bro Cly Met Ala	
40	Met Ala Ala Ala Ala Ala Gly Pro Glu Met Val Arg Gly Gln Val	
40		
	TTC CAC CTC CCC TTC	
	TTC GAC GTG GGG CCG CGC TAC ACT AAT CTC TCG TAC ATC GGA GAA GGC Phe Asp Val Gly Pro Arg Tyr Thr Asp Low Company Tack Act Act GGA GAA GGC 96	
	20 Ash Led Ser Tyr Ile Gly Glu Gly	
45	30	
	GCC TAC GGC ATG GTT TGT TCT GCT TAT GAT AAT CTC AAC AAA GTT CGA 144	
	Ala Tyr Gly Met Val Cys Ser Ala Tyr Asp Asn Leu Asn Lys Val Arg	
	35 40 45	
50		
00	GTT GCT ATC AAG AAA ATC AGT CCT TTT GAG CAC CAG ACC TAC TGT CAG Val Ala Ile Lys Lys Ile Ser Bro Bbs Gl Tyl	
	50 FIG PIE GIU His Gln Thr Tyr Cys Gln	
	60	
	AGA ACC CTG AGA GAG ATA AAA ATC CTA CTG CGC TTC AGA CAT GAG AAC Arg Thr Leu Arg Glu Ile Lys Ile Lou Lau CTG CGC TTC AGA CAT GAG AAC 240	
55	Arg Thr Leu Arg Glu Ile Lys Ile Leu Leu Arg Phe Arg His Glu Asn 70	
	80	
	122	

5		ATC Ile								288
3		GAT Asp								336
10		TTG Leu								384
15		CAG Gln 130								432
20		CGT Arg								480
25		AAG Lys								528
		CAT His								576
30		CCA Pro								624
35		TGG Trp 210								672
40	_	TTC Phe								720
45		CTT Leu								768
		GCT Ala								816
50		AAC Asn								864
55		AAA Lys								912

5	CCC ATT GCT GAA GCA CCA TTG ARG TTT	960
	325 Asp Met Glu Leu Asp Asp Leu 330 335	1008
10	Pro Lys Glu Lys Leu Lys Glu Leu Ile Phe Glu Glu Thr Ala Arg Phe 340 340 345	1056
15	355 360 Pro Pro Val Ala Thr Met Val Ser	1104
20	370 375 380	152
25	385 390 395 File Ser Val Ser Gly Glu Gly Glu	200
	GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC TGC ACC ACC Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile Cys Thr Thr 405 410 415	248
30	GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC CTG ACC TAC Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr Leu Thr Tyr 420 425 430	96
35	GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG AAG CAG CAC GAC Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys Gln His Asp 445	44
40	TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG CGC ACC ATC Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu Arg Thr Ile 450 450	92
45	TTC TTC AAG GAC GAC GGC AAC TAC AAG ACC CGC GCC GAG GTG AAG TTC Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu Val Lys Phe 470 480	10
	GAG GGC GAC ACC CTG GTG AAC CGC ATC GAG CTG AAG GGC ATC GAC TTC 148 Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly Ile Asp Phe 485 490 495	18
50	AAG GAG GAC GGC AAC ATC CTG GGG CAC AAG CTG GAG TAC AAC TAC AAC Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr Asn Tyr Asn 500 505 510	6
55	AGC CAC AAC GTC TAT ATC ATG GCC GAC AAG CAG AAG AAC GGC ATC AAG Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn Gly Ile Lys 515 520 525	4

	GTG	አአሮ	TTC	א א כי	איזיכי	ccc	CAC	7 7 C	איזיכי	CAC	CAC	ccc	200	CTC.	CAC	CTC	1622
			Phe														1632
5	GCC	GAC	CAC	ጥልሮ	CAG	CAG	ממ	A C C	CCC	ስጥሮ	GGC	GNC	ecc	ccc	CTC	CTC	1680
	_		His		_	_											1000
	545					550					555					560	
10	CTG	CCC	GAC	AAC	CAC	TAC	CTG	AGC	ACC	CAG	TCC	GCC	CTG	AGC	AAA	GAC	1728
	Leu	Pro	Asp	Asn	His 565	Tyr	Leu	Ser	Thr	Gln 570	Ser	Ala	Leu	Ser	Lys 575	Asp	
15			GAG Glu														1776
				580	_	_			585					590			
	GCC	GGG	ATC	ACT	CTC	GGC	ATG	GAC	GAG	CTG	TAC	AA (STAA				1815
20	Ala	Gly	Ile 595	Thr	Leu	Gly	Met	Asp 600	Glu	Leu	Tyr	Lys					
			3,7,3					000									
			(2)	INI	FORM	ATION	V FOI	R SEC) ID	NO:	59:						
05																	
25		(:	i) SI (A)	-		604											
						nino											
						ONESS 7: 1:		_	=								
30																	
			ii) N v) FI				-							٠			
		(3	(i) 9	SEOUE	ENCE	DESC	ים ד קי	rton -	950	מד נ	NO ·	; a .					
35																	
	Met 1	Ala	Ala	Ala	Ala 5	Ala	Ala	Gly	Pro	Glu 10	Met	Val	Arg	Gly	Gln 15	Val	
		Asp	Val	Gly	_	Arg	Tyr	Thr	Asn		Ser	Tyr	Ile	Gly		Gly	
40	Ala	Tvr	Gly	20 Met	Val	Cve	Ser	Δla	25 Tyr	Agn	Aen	T.611	Δen	30 Lve	Val	Ara	
			35					40					45				
	Val	Ala 50	Ile	Lys	Lys	Ile	Ser 55	Pro	Phe	Glu	His	Gln 60	Thr	Tyr	Cys	Gln	
4.5		-	Leu	Arg	Glu			Ile	Leu	Leu			Arg	His	Glu		
45	65 Ile	Ile	Gly	Ile	Asn	70 Asp	Ile	Ile	Arg	Ala	75 Pro	Thr	Ile	Glu	Gln	80 Met	
					85					90					95		
	nys	Авр	Val	1yr 100	тте	val	GIN	Asp	Leu 105	met	GIU	Tnr	Asp	Leu 110	Tyr	пуѕ	
50	Leu	Leu	Lys 115	Thr	Gln	His	Leu	Ser 120	Asn	Asp	His	Ile	Cys 125	Tyr	Phe	Leu	
	Tyr		Ile	Leu	Arg	Gly	Leu		Tyr	Ile	His	Ser		Asn	Val	Leu	
		1 7 0					135					140					
	His	130 Ara	Asp	Leu	Lvs	Pro		Agn	Len	T.e.	Leu		Thr	Thr	Cve	Agn	
55	145	Arg	Asp Ile			150	Ser				155	Asn				160	

														126								
	λ	en	u:	~ ~	h c		165							170	0					1	.75	
			- 1	.s r	nr c	80 TÀ	Phe	: Le	eu T	hr	G1	u T 1	yr 85	Va:	l A	la 1	hr	Ar	g T:	rp 1 0e	'nг	Arg
5																						Asp
																		Se	r As			Pro
																u A						Gly
10	IJ	le	Le	u G	ly s	er :	Pro 245	Se	r G	ln	Glı	1 A:	ge	Leu	23 As	n C	ys	Ile	: Il	e A	sn	240 Leu
					g A							: Le	≥u									
15					g L					n	Ala	As										
					t Le				e As	n												
					a Hi				r Le													
20					a Gl	u A							e .	qaA								
					u Ly 34	s L						11	e j									
25					у Ту					t i	Asp											
					u Gl				Th	r												
					o Va		sn (His													
30					a Th	r Ty							: L	eu.								
					Pro							Thi	- 4.									
35					Cys					T	yr											
					Ser				Pro	G												
	Phe 465	P	he	Lys	Asp	As	рG	1y 70	455 Asn	T	yr	Lys	T	hr A	Arg	460 Ala) a G	lu	Val	Lys	P	he
40	Glu	G.	ly	Asp	Thr	Le	u V	al	Asn	A:	rg	Ile	G.	lu I	175 Leu	Lys	G.	ly	Ile	Asp	4 P	80 he
	Lys	G.	lu	Asp	Gly 500	As	n I	le	Leu	G.	ly :	His	4: Ly	ys I	eu	Glu	T	yr i	Asn	495 Tyr	A	sn
45	Ser	Hi	is .	Asn 515	Val	ту	r I	le	Met	A)	la 2 20	Asp	ΓŽ	/s G	ln	Lys	As	sn (510 3ly	Ile	L	ys
	Val	As 53	n 30	Phe	Lys	Il	e A:	rg	His 535	As	n :	Ile	G)	lu A	sp	Gly	52 Se	25 er V	/al	Gln	Le	eu
	Ala 545	As	gp)	His	Tyr	Glı	a G	ln .	Asn	Th	ır I	Pro	11	le G	ly	540 Asp	G]	ly I	ro	Val	Le	eu
50	Leu	Pr	O 1	Asp	Asn	His 569	Ty	/r :	Leu	Se	rı	hr	G1	n S	er	Ala	Le	u S	er	Lys	5 <i>6</i> As	50 Sp
	Pro	As	n (3lu	Lys 580	Arg	j As	p l	His	Me	t V	al	Le	u L	eu	Glu	Ph	e V	al	575 Thr	Al	.a
55	Ala	Gl	у 1	le 595	Thr	Lev	G]	у 1	Met	As 60	p q	85 1u	Le	u T	yr .	Lys		5	90			

(2) INFORMATION FOR SEQ ID NO:60:

127

5	(A) LEN (B) TYP (C) STR	NCE CHARACTERI GTH: 2511 base E: nucleic aci ANDEDNESS: sin OLOGY: linear	e pairs id												
10	(ii) MOLE (ix) FEAT	CULE TYPE: cDN URE:	AI												
15	(A) NAME/KEY: Coding Sequence (B) LOCATION: 12508 (D) OTHER INFORMATION: (xi) SEQUENCE DESCRIPTION: SEQ ID NO:60: ATG GAG CTG GAA AAC ATC GTG GCC AAC ACG GTC TTG CTG AAA GCC AGG														
20	ATG GAG CTG GAA Met Glu Leu Glu 1														
25	GAA GGG GGC GGA Glu Gly Gly Gly 20														
20	ATC CTG AAG TTC Ile Leu Lys Phe 35	Pro His Ile S													
30	ATA GAC AGA GAT Ile Asp Arg Asp 50														
35	CTG CTT TTC CGG Leu Leu Phe Arg 65														
40	ATT CAG TTC CTG Ile Gln Phe Leu														

ACG GAG GAG AAG CTC CTA CAG AAG CCG TGC AAA GAA CTC TTT TCT GCC

Thr Glu Glu Lys Leu Leu Gln Lys Pro Cys Lys Glu Leu Phe Ser Ala

130

TGT GCA CAG TCT GTC CAC GAG TAC CTG. AGG GGA GAA CCA TTC CAC GAA

Cys Ala Gln Ser Val His Glu Tyr Leu Arg Gly Glu Pro Phe His Glu

145

150

155

160

AAA CTG GGA GAG AAA GGG AAG GAA ATT ATG ACC AAG TAC CTC ACC CCA

Lys Leu Gly Glu Lys Gly Lys Glu Ile Met Thr Lys Tyr Leu Thr Pro

AAG TCC CCT GTT TTC ATA GCC CAA GTT GGC CAA GAC CTG GTC TCC CAG

Lys Ser Pro Val Phe Ile Ala Gln Val Gly Gln Asp Leu Val Ser Gln 115 120 125

105

100

45

50

55

127

336

5		eu
	GAA AGG CAA CCG GTG ACC AAA AAC ACT TTC AGG CAG TAT CGA GTG CT Glu Arg Gln Pro Val Thr Lys Asn Thr Phe Arg Gln Tyr Arg Val Le 180 185 190	TA 576 eu
10	Gly Lys Gly Phe Gly Glu Val Cys Ala Cys Gln Val Arg Ala Th	r
15	210 215 Lys Arg Leu Glu Lys Lys Arg Ile Lys Ly	s
20	230 235 240	s D
25	GTC AAC AGT CAG TTT GTG GTC AAC CTG GCC TAT GCC TAC GAG ACC AAC Val Asn Ser Gln Phe Val Val Asn Leu Ala Tyr Ala Tyr Glu Thr Lys 245 250 255	3
	GAT GCA CTG TGC TTG GTC CTG ACC ATC ATG AAT GGG GGT GAC CTG AAG Asp Ala Leu Cys Leu Val Leu Thr Ile Met Asn Gly Gly Asp Leu Lys 260 265 270	•
30	TTC CAC ATC TAC AAC ATG GGC AAC CCT GGC TTC GAG GAG GAG CGG GCC Phe His Ile Tyr Asn Met Gly Asn Pro Gly Phe Glu Glu Glu Arg Ala 275 280 285	864
35	TTG TTT TAT GCG GCA GAG ATC CTC TGC GGC TTA GAA GAC CTC CAC CGT Leu Phe Tyr Ala Ala Glu Ile Leu Cys Gly Leu Glu Asp Leu His Arg 290 295 300	912
40	GAG AAC ACC GTC TAC CGA GAT CTG AAA CCT GAA AAC ATC CTG TTA GAT Glu Asn Thr Val Tyr Arg Asp Leu Lys Pro Glu Asn Ile Leu Leu Asp 305 310 315 320	960
45	GAT TAT GGC CAC ATT AGG ATC TCA GAC CTG GGC TTG GCT GTG AAG ATC Asp Tyr Gly His Ile Arg Ile Ser Asp Leu Gly Leu Ala Val Lys Ile 325	1008
	CCC GAG GGA GAC CTG ATC CGC GGC CGG GTG GGC ACT GTT GGC TAC ATG Pro Glu Gly Asp Leu Ile Arg Gly Arg Val Gly Thr Val Gly Tyr Met 340 345 350	1056
50	GCC CCC GAA GTC CTG AAC AAC CAG AGG TAC GGC CTG AGC CCC GAC TAC Ala Pro Glu Val Leu Asn Asn Gln Arg Tyr Gly Leu Ser Pro Asp Tyr 355 360 365	1104
55	TGG GGC CTT GGC TGC CTC ATC TAT GAG ATG ATC GAG GGC CAG TCG CCG Trp Gly Leu Gly Cys Leu Ile Tyr Glu Met Ile Glu Gly Gln Ser Pro 370 380	1152

5		_		AAG Lys	_	_					1200
-				GAG Glu 405							1248
10				AAG Lys							1296
15				GAG Glu							1344
20				TTC Phe							1392
25				ccc Pro							1440
				ACT Thr 485							1488
30				AAG Lys							1536
35				GAA Glu						_	1584
40				CTC Leu							1632
45				GGG Gly							1680
				AGT Ser 565							1728
50				CAT His							1776
55		_	_	ACC Thr						_	1824

5	610		615	u Asp Gly	GAC GTA AAC (Asp Val Asn (620	Sly His Lys	1872
	TTC AGC GT Phe Ser Va. 625	, -	AG GGC GAG lu Gly Gli 30	G GGC GAT u Gly Asp	GCC ACC TAC G Ala Thr Tyr G	GC AAG CTG Ly Lys Leu 640	1920
10	•	645	ys Int In	650	CTG CCC GTG C Leu Pro Val P	ro Trp Pro 655	1968
15		660	ou int tyt	665		er Arg Tyr 70	2016
20	675	i	680	Phe Phe	AAG TCC GCC A Lys Ser Ala Me 685	et Pro Glu	2064
25	690		695	Phe Phe 1	AAG GAC GAC GC Lys Asp Asp Gl 700	y Asn Tyr	2112
20	705	71	o Lys Phe	GIU GIY A	GAC ACC CTG GT Asp Thr Leu Va 715	l Asn Arg 720	2160
30		725	- wah bue	730	GAC GGC AAC AT asp Gly Asn Il	e Leu Gly 735	2208
35		740	· 171 ASII	745	AC GTC TAT ATO sn Val Tyr Ilo 750	e Met Ala)	2256
40	GAC AAG CAG Asp Lys Gln 755	AAG AAC GGC Lys Asn Gly	ATC AAG Ile Lys 760	GTG AAC T Val Asn Pl	TC AAG ATC CGG he Lys Ile Arg 765	C CAC AAC His Asn	2304
45	770	7	775	Ala Asp Hi	AC TAC CAG CAG is Tyr Gln Gln 780	Asn Thr	2352
	785	790	var neu I	Leu Pro As 79		Leu Ser 800	2400
50		805	rya wah P	810	G AAG CGC GAT u Lys Arg Asp	His Met 815	2448
55	GTC CTG CTG G Val Leu Leu G 8	AG TTC GTG lu Phe Val	INI AIA A	CC GGG AT la Gly Il 25	C ACT CTC GGC e Thr Leu Gly 830	ATG GAC Met Asp	2496

131

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GAG CTG TAC AAG TAA
                                                                 2511
     Glu Leu Tyr Lys
           835
5
             (2) INFORMATION FOR SEQ ID NO:61:
          (i) SEQUENCE CHARACTERISTICS:
10
            (A) LENGTH: 836 amino acids
            (B) TYPE: amino acid
            (C) STRANDEDNESS: single
            (D) TOPOLOGY: linear
15
          (ii) MOLECULE TYPE: protein
          (v) FRAGMENT TYPE: internal
          (xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:
20
     Met Glu Leu Glu Asn Ile Val Ala Asn Thr Val Leu Leu Lys Ala Arg
                 5
                           10
     Glu Gly Gly Gly Lys Arg Lys Gly Lys Ser Lys Lys Trp Lys Glu
               20
                               25
     Ile Leu Lys Phe Pro His Ile Ser Gln Cys Glu Asp Leu Arg Arg Thr
25
                             40
     Ile Asp Arg Asp Tyr Cys Ser Leu Cys Asp Lys Gln Pro Ile Gly Arg
     Leu Leu Phe Arg Gln Phe Cys Glu Thr Arg Pro Gly Leu Glu Cys Tyr
            70
                                        75
30
     Ile Gln Phe Leu Asp Ser Val Ala Glu Tyr Glu Val Thr Pro Asp Glu
                                    90
     Lys Leu Gly Glu Lys Gly Lys Glu Ile Met Thr Lys Tyr Leu Thr Pro
              100
                      105 110
     Lys Ser Pro Val Phe Ile Ala Gln Val Gly Gln Asp Leu Val Ser Gln
35
                             120
                                               125
     Thr Glu Glu Lys Leu Leu Gln Lys Pro Cys Lys Glu Leu Phe Ser Ala
        130 135
                                           140
     Cys Ala Gln Ser Val His Glu Tyr Leu Arg Gly Glu Pro Phe His Glu
                      150
                                        155 160
40
     Tyr Leu Asp Ser Met Phe Phe Asp Arg Phe Leu Gln Trp Lys Trp Leu
                  165
                                    170
                                                      175
     Glu Arg Gln Pro Val Thr Lys Asn Thr Phe Arg Gln Tyr Arg Val Leu
                                 185
               180
     Gly Lys Gly Gly Phe Gly Glu Val Cys Ala Cys Gln Val Arg Ala Thr
45
           195
                             200
                                               205
     Gly Lys Met Tyr Ala Cys Lys Arg Leu Glu Lys Lys Arg Ile Lys Lys
                215 220
     Arg Lys Gly Glu Ser Met Ala Leu Asn Glu Lys Gln Ile Leu Glu Lys
                      230
50
     Val Asn Ser Gln Phe Val Val Asn Leu Ala Tyr Ala Tyr Glu Thr Lys
                          250
                  245
     Asp Ala Leu Cys Leu Val Leu Thr Ile Met Asn Gly Gly Asp Leu Lys
                                 265
     Phe His Ile Tyr Asn Met Gly Asn Pro Gly Phe Glu Glu Glu Arg Ala
55
                              280
     Leu Phe Tyr Ala Ala Glu Ile Leu Cys Gly Leu Glu Asp Leu His Arg
```

								132					
		90			29	5				300			
		sn Thr								Asn]			
5		yr Gly		le Ar	g Il				Gly				
	Pro G	lu Gly	Asp I	eu Il	e Ar	g Gly	Arg	Val	Gly	Thr V	al Gl	33 y Ty	5 r Met
	Ala P	ro Glu 355	Val L	eu As	n Ası	n Gln	345 Arg	Tyr	Gly	Leu S	35 er Pr	0 O As	p Tyr
10		ly Leu 70			u Ile	oou Tyr							
	Phe A:	rg Gly	Arg L	ys Gl 39	u Lys	v Val	Lys	Arg	Glu	380 Glu V	al As	p Ar	g Arg
15		eu Glu	Thr G					His					
		er Ile					Thr						
		s Gln 435				Ala							
20		n Met			arg	Leu							
		l Pro			, Ala			Cys :	4 Lys A				
	Glu Gl												
25	Asp Ph												
	Asn Gl												
30	Pro Ası												
	530 Pro Pro 545												
35	Asn Asr												
	Ile Asr												
40	Pro Pro										ı Phe		
	Val Val 610	Val a	re ren	val	Glu 615	Leu A	sp G	ly A	sp Va 62	l Asr	Gly	His	Lys
	Phe Ser 625	Val S	er Gly	630	Gly	Glu G	ly A	sp Al	la Th 35	r Tyr	Gly	Lys	Leu 640
45	Thr Leu												
	Thr Leu											Arg	
50	Pro Asp												
	Gly Tyr 690 Lys Thr												
	Lys Thr 705 Ile Glu												
55	Ile Glu His Lys												
	His Lys	_	-1-		-у. А	.a.i 56	r HI	S AS	n Va]	Tyr	Ile 1	Met A	lla

				740					745					750				
	Asp	Lys	Gln 755	Lys	Asn	Gly	Ile	Lys 760	Val	Asn	Phe	Lys	Ile 765	Arg	His	Asn		
5	Ile	Glu 770	Asp	Gly	Ser	Val	Gln 775	Leu	Ala	Asp	His	Tyr 780	Gln	Gln	Asn	Thr		
	785			Asp	_	790					795			_		800		
	Thr	Gln	Ser	Ala	Leu 805	Ser	Lys	Asp	Pro	Asn 810	Glu	Lys	Arg	Asp	His 815	Met		
10	Val	Leu	Leu	Glu 820	Phe	Val	Thr	Ala	Ala 825	Gly	Ile	Thr	Leu	Gly 830	Met	Asp		
	Glu	Leu	Tyr 835	Lys														
15			(2)	INI	FORM	OITA	FOI	SE(O ID	NO: 6	52:							
		()		EQUEN														
20			(B)	TYPE	ີ: ກເ	ıclei	c a	cid										
20				TOPO				~	-									
				OLEC FEATU		TYPE	E: cI	ANO										
25			(A)	NAN	Æ/KI	EY: (Codir	ıg Se	equer	ıce								
	(A) NAME/KEY: Coding Sequence(B) LOCATION: 11890(D) OTHER INFORMATION:														•			
30		()	(i) S	EQUI	ENCE	DESC	RIPT	rion	: SE(O ID	NO : 6	52:						
				AGC													48	
35	1	561	Arg	Ser	5	n. y	vah	ASII	ASII	10	Tyr	361	vaı	Giu	15	GIY		
00				TTC Phe												_	96	
				20				-1-	25	-1-				30				
40				GCT Ala													144	
			35					40	-			-	45					
45				GTT Val													192	
		50					55					60						
50	Thr			AAG Lys		Ala					Val					Val	240	
50	65					70					75					80		
				AAT Asn	Ile					Asn					Gln		288	
55	тсс	ርጥኔ	GAD	GAA	85 TTT	CDD	GAT	Con	тъс	90 ara	ርጥር	ልጥር፡	GAG	CTC	95 atg	САТ	336	
	100		JAA	UAM		SAL	UA1	011	INC	SIM	010	0	UAG		AIG	U,11		133

									•			34								
	Se	r L	eu G	lu G 1	lu 1 00	Phe	Gln	Asp	V a	1 T	yr : 05	lle	Va]	Met	: G1		eu 1 10	Met	Asp	
5			1	15			vui	116	12	0	יב נ	ilu	Leu	Asp	12	s G: 5	lu A	۱rg	ATG Met	384
10	TCC Ser	TA Ty 13	C C' T Le	IT C' ∋u Le	FC I eu I	AT (CAG Gln	ATG Met 135	ье	G ТО	T G	GA ly	ATC Ile	AAG Lys 140	His	C CI	TT C	CAT	TCT Ser	432
15	145		•	T AT]	.50	Asp	пет	тру	s P	ro	Ser 155	Asn	Ile	e Va	1 V	al	Lys 160	480
			,	C AC	1	65	y s	116	тес	l As	р Рі 1'	ne 70	Gly	Leu	Ala	Ar	g T	hr 75	Ala	528
20	-			T TT r Ph 18	0	11	C.C.	TILL	Pro	185	r Va	al ,	Val	Thr	Arg	Ту: 19	r Ty	yr	Arg	576
25	GCA Ala	Pro	GA6 Gli 19!	G GT u Va. 5	C AT	CC C	TT (GGC Gly	ATG Met 200	GG(TA Ty	C A	AAG Lys	GAA Glu	AAC Asn 205	GT(G GA	T.	TTA Leu	624
30	TGG Trp	TCT Ser 210	Va]	GGG Gly	Э ТС У Су	C A		ATG let	GGA Gly	GAA Glu	AT Me	G G t V	al	TGC Cys 220	CAC His	AAA Lys	AT Il	C (CTC Leu	672
35	TTT Phe 225	CCA Pro	GGA Gly	AGO Arg	G GA J As	С ТА р Ту 23	т т	TT (GAT Asp	CAG Gln	TG Tr	pΑ	AT i sn 1	AAA Lys	GTT Val	ATT Ile	GA G1	u C	CAG Sln 240	720
	CTT (GGA Gly	ACA Thr	CCA Pro	TG: Cy: 24!	3 F.L	T G	AA : lu I	rrc Phe	ATG Met	AA(Lys 25(3 L	AA (ys I	CTG (Leu (CAA Gln	CCA Pro	AC. Th:	r V	TA al	768
40	AGG A	ACT Thr	TAC Tyr	GTT Val 260		A AA 1 As	C A	GA (rg F	10	AAA Lys 265	ТАТ	r Go	CT G la G	GA 7	yr	AGC Ser 270	TT:	ΓG e G	AG lu	816
45	AAA (CTC Leu	TTC Phe 275	CCT Pro	GAT Asp	GT(C CI	eu P	TC he 80	CCA Pro	GCT Ala	GA As	AC T sp s	er G	AA (CAC His	AA(Asr	C A	AA ys	864
50	CTT A Leu L 2	AA ys 90	GCC Ala	AGT Ser	CAG Gln	GCA Ala	A Ac a Ar 29	y A	AT 1	TTG Leu	TTA Leu	TC Se	r L	AA A ys M	TG (et I	CTG Seu	GTA Val	A. A.	ΓA le	912
55	GAT G Asp A 305	CA la	TCT Ser	AAA Lys	AGG Arg	ATC Ile 310		T G	TA (GAT Asp	GAA Glu	GC Al 31	a Le	TC C. eu G.	AA C ln H	CAC Iis	CCG Pro	ТД Ту 32	r	960
	ATC A	AT (GTC	TGG	TAT	GAT	CC	т т	CT G	SAA (GCA	GA	A GO	CT C	CA C	CA	CCA	AA	.G	1008

										135							
	Ile	Asn	Val	Trp	Tyr 325	Asp	Pro	Ser	Glu	Ala 330	Glu	Ala	Pro	Pro	Pro 335	Lys	
5		CCT Pro															1056
10		GAA Glu															1104
15		GGA Gly 370															1152
		GAT Asp															1200
20		GGG Gly	_			_											1248
25		AAG Lys															1296
30		CTG Leu															1344
35		CCC Pro 450															1392
		TAC Tyr															1440
40		GAA Glu															1488
45		TAC Tyr															1536
50		CGC Arg															1584
55		GGG Gly 530															1632
	ATG	GCC	GAC	AAG	CAG	AAG	AAC	GGC	ATC	AAG	GTG	AAC	TTC	AAG	ATC	CGC	1680

	136	
	Met Ala Asp Lys Gln Lys Asn Gly Ile Lys Val Asn Phe Lys Ile Arg 545 550 560	
5	CAC AAC ATC GAG GAC GGC AGC GTG CAG CTC GCC GAC CAC TAC CAG CAG His Asn Ile Glu Asp Gly Ser Val Gln Leu Ala Asp His Tyr Gln Gln 565 570 575	1728
10	AAC ACC CCC ATC GGC GAC GGC CCC GTG CTG CTG CCC GAC AAC CAC TAC Asn Thr Pro Ile Gly Asp Gly Pro Val Leu Pro Asp Asn His Tyr 580 585 590	1776
15	CTG AGC ACC CAG TCC GCC CTG AGC AAA GAC CCC AAC GAG AAG CGC GAT Leu Ser Thr Gln Ser Ala Leu Ser Lys Asp Pro Asn Glu Lys Arg Asp 595 600 605	1824
	CAC ATG GTC CTG GAG TTC GTG ACC GCC GGG ATC ACT CTC GGC His Met Val Leu Leu Glu Phe Val Thr Ala Ala Gly Ile Thr Leu Gly 610 620	1872
20	ATG GAC GAG CTG TAC AAG TAA Met Asp Glu Leu Tyr Lys 625 630	1893
25	(2) INFORMATION FOR SEQ ID NO:63:	
30	 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 630 amino acids (B) TYPE: amino acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 	
35	(ii) MOLECULE TYPE: protein(v) FRAGMENT TYPE: internal(xi) SEQUENCE DESCRIPTION: SEQ ID NO:63:	
	Met Ser Arg Ser Lys Arg Asp Asn Asn Phe Tyr Ser Val Glu Ile Gly	
40	Asp Ser Thr Phe Thr Val Leu Lys Arg Tyr Gln Asn Leu Lys Pro Ile	
-	Gly Ser Gly Ala Gln Gly Ile Val Cys Ala Ala Tyr Asp Ala Ile Leu	
45	Glu Arg Asn Val Ala Ile Lys Lys Leu Ser Arg Pro Phe Gln Asn Gln	
	Thr His Ala Lys Arg Ala Tyr Arg Glu Leu Val Leu Met Lys Cys Val 65 70 75 80 Asn His Lys Asn Ile Ile Gly Leu Leu Asn Val Phe Thr Pro Gln Lys	
50	Ser Leu Glu Glu Phe Gln Asp Val Tyr Ile Val Met Glu Leu Met Asp	
	Ala Asn Leu Cys Gln Val Ile Gln Met Glu Leu Asp His Glu Arg Met	
55	Ser Tyr Leu Leu Tyr Gln Met Leu Cys Gly Ile Lys His Leu His Ser	
	Ala Gly Ile Ile His Arg Asp Leu Lys Pro Ser Asn Ile Val Val Lys	120

	145					150					155					160
	Ser	Asp	Cys	Thr	Leu 165	Lys	Ile	Leu	Asp	Phe 170	Gly	Leu	Ala	Arg	Thr 175	Ala
5	Gly	Thr	Ser	Phe 180	Met	Met	Thr	Pro	Tyr 185	Val	Val	Thr	Arg	Tyr 190	Tyr	Arg
	Ala	Pro	Glu 195	Val	Ile	Leu	Gly	Met 200	Gly	Tyr	Lys	Glu	Asn 205	Val	Asp	Leu
	Trp	Ser 210	Val	Gly	Суз	Ile	Met 215	Gly	Glu	Met	Val	Cys 220	His	Lys	Ile	Leu
10	Phe 225	Pro	Gly	Arg	Asp	Tyr 230	Ile	Asp	Gln	Trp	Asn 235	Lys	Val	Ile	Glu	Gln 240
	Leu	Gly	Thr	Pro	Cys 245	Pro	Glu	Phe	Met	Lys 250	Lys	Leu	Gln	Pro	Thr 255	Val
15	Arg	Thr	Tyr	Val 260	Glu	Asn	Arg	Pro	Lys 265	Tyr	Ala	Gly	Tyr	Ser 270	Phe	Glu
	Lys	Leu	Phe 275	Pro	Asp	Val	Leu	Phe 280	Pro	Ala	Asp	Ser	Glu 285	His	Asn	Lys
	Leu	Lys 290	Ala	Ser	Gln	Ala	Arg 295	Asp	Leu	Leu	Ser	Lys 300	Met	Leu	Val	Ile
20	Asp 305	Ala	Ser	Lys	Arg	Ile 310	Ser	Val	Asp	Glu	Ala 315	Leu	Gln	His	Pro	Tyr 320
	Ile	Asn	Val	Trp	Tyr 325	Asp	Pro	Ser	Glu	Ala 330	Glu	Ala	Pro	Pro	Pro 335	Lys
25				340	Gln		_		345					350		_
	Lys	Glu	Leu 355	Ile	Tyr	Lys	Glu	Val 360	Met	Asp	Leu	Glu	Glu 365	Arg	Thr	Lys
	Asn	Gly 370	Val	Ile	Arg	Gly	Gln 375	Pro	Ser	Pro	Leu	Ala 380	Gln	Val	Gln	Gln
30	385	_			Val	390					395	-				400
					Pro 405					410	_		_		415	
35		_		420	Val				425		-	_		430	-	-
	_		435		Lys			440			-	-	445			
40		450			Val		455			_	_	460		-		
40	465			_	His	470	_			_	475		_			480
					Val 485					490					495	
45				500	Arg				505					510		
			515		Leu			520					525			
-50		530			Leu		535					540				
-50	545		_	-	Gln	550		_		-	555			-		560
					565 Gly					570					575	
55				580	Ser				585				_	590		-
							4		-,-					-, -	*** 9	p

	138	
	595 600 605	
	His Met Val Leu Leu Glu Phe Val Thr Ala Ala Gly Ile Thr Leu Gly	
5	Met Asp Glu Leu Tyr Lys	
	630	
	(2) INFORMATION FOR SEQ ID NO:64:	
	(i) SEQUENCE CHARACTERISTICS:	
10	(A) LENGTH: 1821 base pairs	
	(B) TYPE: nucleic acid	
	(C) STRANDEDNESS: single	
	(D) TOPOLOGY: linear	
15	(ii) MOLECULE TYPE: cDNA	
	(ix) FEATURE:	
	(a)	
	(A) NAME/KEY: Coding Sequence	
20	(B) LOCATION: 11818 (D) OTHER INFORMATION:	
ι	(5) STILL INFORMATION:	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:64:	
25	ATG TCT CAG GAG AGG CCC ACG TTC TAC CGG CAG GAG CTG AAC AAG ACA	48
	1 In the lyr Arg GIn Glu Leu Asn Lys Thr	
	10 15	
	ATC TGG GAG GTG CCC GAG CGT TAC CAG AAC CTG TCT CCA GTG GGC TCT	
30	Arg Tyr Gin Ash Leu Ser Pro Val Cly Com	96
00	20 25 30	
	GGC GCC TAT GGC TCT GTG TCT GCT GCT GCT	
	GGC GCC TAT GGC TCT GTG TGT GCT GCT TTT GAC ACA AAA ACG GGG TTA Gly Ala Tyr Gly Ser Val Cys Ala Ala Phe Asp Thr Lys Thr Gly Leu	144
35	40 45 The Asp The Lys Thr Gly Leu	
33		
	CGT GTG GCA GTG AAG AAG CTC TCC AGA CCA TTT CAG TCC ATC ATT CAT	192
	50 Fe Ser Arg Pro Phe Gln Ser Ile Ile His	
40	60	
40	GCG AAA AGA ACC TAC AGA GAA CTG CGG TTA CTT AAA CAT ATG AAA CAT	240
	65 The let Arg Let Let Lys His Met Lys His	240
	70 75 80	
	GAA AAT GTG ATT GGT CTG TTG GAC GTT TTT ACA CCT GCA AGG TCT CTG	
45	Glu Asn Val Ile Gly Leu Leu Asp Val Phe Thr Pro Ala Arg Ser Leu	288
	85 90 95	
	GAG GAA TTC AAT GAT GTG TAT CTG GTG ACC CAT CTC ATG GGG GCA GAT Glu Glu Phe Asn Asp Val Tyr Leu Val Thr His Leu Met Gly Ala Asp	336
50		
	110	
	CTG AAC AAC ATT GTG AAA TGT CAG AAG CTT ACA GAT GAC CAT GTT CAG	384
	115 Cys Gin Lys Leu Thr Asp Asp His Val Gln	201
55	120 125	
	TTC CTT ATC TAC CAA ATT CTC CGA GGT CTA AAG TAT ATA CAT TCA GCT	
	AIR CAI FCA GCT	432
		138

										139							
	Phe	Leu 130	Ile	Tyr	Gln	Ile	Leu 135	Arg	Gly	Leu	Lys	Tyr 140	Ile	His	Ser	Ala	
5					AGG Arg												480
10					AAG Lys 165												528
15					GGC Gly									_		_	576
13					TGG Trp												624
20					ATG Met												672
25					ATT Ile												720
30					GAG Glu 245												768
35					TCT Ser										_		816
33					GCC Ala												864
40					TCA Ser									_		_	912
45					GCT Ala												960
50					CAG Gln 325											_	1008
55					ACC Thr												1056
55	CTT	GAC	CAA	GAA	GAG	ATG	GAG	TCC	GAG	GAT	CCA	CCG	GTC	GCC	ACC	ATG	1104

	140	
	Leu Asp Gln Glu Glu Met Glu Ser Glu Asp Pro Pro Val Ala Thr Met 355 360 365	
5	GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG GTC Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu Val 370 380	1152
10	GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC GAG Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly Glu 385 390 395 400	1200
15	GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC TGC Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile Cys 405 410	1248
	ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC CTG Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr Leu 420 425 430	1296
20	ACC TAC GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG AAG CAG Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys Gln 435 440 445	1344
25	CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG CGC His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu Arg 450 455 460	1392
30	ACC ATC TTC TTC AAG GAC GAC GGC AAC TAC AAG ACC CGC GCC GAG GTG Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu Val 465 470 475 480	1440
35	AAG TTC GAG GGC GAC ACC CTG GTG AAC CGC ATC GAG CTG AAG GGC ATC Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly Ile 485 490 495	1488
	GAC TTC AAG GAG GAC GGC AAC ATC CTG GGG CAC AAG CTG GAG TAC AAC Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr Asn 505 510	1536
40	TAC AAC AGC CAC AAC GTC TAT ATC ATG GCC GAC AAG CAG AAG AAC GGC Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn Gly 515 520 525	1584
45	ATC AAG GTG AAC TTC AAG ATC CGC CAC AAC ATC GAG GAC GGC AGC GTG Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser Val 530 540	1632
50	CAG CTC GCC GAC CAC TAC CAG CAG AAC ACC CCC ATC GGC GAC GGC CCC Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly Pro 555 560	1680
55	GTG CTG CTG CCC GAC AAC CAC TAC CTG AGC ACC CAG TCC GCC CTG AGC Val Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu Ser 575	1728
	AAA GAC CCC AAC GAG AAG CGC GAT CAC ATG GTC CTG GAG TTC GTG	1776

141

Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe Val 580 585 ACC GCC GCC GGG ATC ACT CTC GGC ATG GAC GAG CTG TAC AAG TAA 1821 5 Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys 595 600 (2) INFORMATION FOR SEQ ID NO:65: 10 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 606 amino acids (B) TYPE: amino acid (C) STRANDEDNESS: single 15 (D) TOPOLOGY: linear (ii) MOLECULE TYPE: protein (v) FRAGMENT TYPE: internal 20 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:65: Met Ser Gln Glu Arg Pro Thr Phe Tyr Arg Gln Glu Leu Asn Lys Thr 5 10 Ile Trp Glu Val Pro Glu Arg Tyr Gln Asn Leu Ser Pro Val Gly Ser 25 20 25 Gly Ala Tyr Gly Ser Val Cys Ala Ala Phe Asp Thr Lys Thr Gly Leu 40 45 Arg Val Ala Val Lys Lys Leu Ser Arg Pro Phe Gln Ser Ile Ile His 30 Ala Lys Arg Thr Tyr Arg Glu Leu Arg Leu Leu Lys His Met Lys His 70 75 Glu Asn Val Ile Gly Leu Leu Asp Val Phe Thr Pro Ala Arg Ser Leu 85 90 Glu Glu Phe Asn Asp Val Tyr Leu Val Thr His Leu Met Gly Ala Asp 100 105 110 35 Leu Asn Asn Ile Val Lys Cys Gln Lys Leu Thr Asp Asp His Val Gln 120 Phe Leu Ile Tyr Gln Ile Leu Arg Gly Leu Lys Tyr Ile His Ser Ala 135 140 40 Asp Ile Ile His Arg Asp Leu Lys Pro Ser Asn Leu Ala Val Asn Glu 155 Asp Cys Glu Leu Lys Ile Leu Asp Phe Gly Leu Ala Arg His Thr Asp 165 170 175 Asp Glu Met Thr Gly Tyr Val Ala Thr Arg Trp Tyr Arg Ala Pro Glu 45 185 190 Ile Met Leu Asn Trp Met His Tyr Asn Gln Thr Val Asp Ile Trp Ser 195 200 205 Val Gly Cys Ile Met Ala Glu Leu Leu Thr Gly Arg Thr Leu Phe Pro 215 220 50 Gly Thr Asp His Ile Asp Gln Leu Lys Leu Ile Leu Arg Leu Val Gly 230 235 Thr Pro Gly Ala Glu Leu Leu Lys Lys Ile Ser Ser Glu Ser Ala Arg 245 250

141

Asn Tyr Ile Gln Ser Leu Thr Gln Met Pro Lys Met Asn Phe Ala Asn

Val Phe Ile Gly Ala Asn Pro Leu Ala Val Asp Leu Leu Glu Lys Met

265

260

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										142	?					
	_		275					28	0				28	E		
	Leu	Val 290	Let	ı Asp) Se	r As	р Ly 29	s Ar 5	g Il	e Th	r Al	a Al.	a Gl	n Al	a Le	u Ala
5	His 305	Ala	Туг	Phe	≥ Ala	G1 31	n Ty	r Hi	s As	p Pr	o Ası	As ₁	o o Gli	u Pr	o Va	l Ala
	Asp	Pro	Tyr	Asp	Glr 325	se:	r Ph	e Gl	u Se	r Ar	g Asp	5 Let	ı Leı	u Ile	e As	320 Glu
	Trp	Lys	Ser	Leu 340	Thr	Ty:	r Ası	o Glu	ı Va	330 1 Ile) ≥ Ser	Phe	va]	l Pro	33! Pro	5 Pro
10	· Leu	Asp	Gln	Glu	Glu	Met	t Glu	ı Seı	345 Glu	5 1 Asp	Pro) Pro	Va]	350 Ala) a Thi	Met
	Val	Ser	Lys	Gly	Glu	Glu	ı Lev	360 Phe) Thi	c Gly	, Val	Val	365 Pro	i Tle	· Lei	val
	Glu	370	A ===	0 3	_		375	i		-		380		, 110	, Der	, val
15	385	neu	Asp	GIY	Asp	Val	Asn	ı Gly	His	Lys	Phe	Ser	Val	Ser	Gly	Glu
	Thr	Glu Thr	Gly	Lvs	405 Leu	Pro	Val	GIY	цуs	410	Thr	Leu	Lys	Phe	1le 415	Cys
20	Thr	Thr Tvr	Glv	420 Val	Gln	Cira	Db-	PIO	425	Pro	Thr	Leu	Val	Thr 430	Thr	Leu
	His	Tyr Asp	435 Phe	Phe	Lve	Cys	Al-	440	Arg	Tyr	Pro	Asp	His 445	Met	Lys	Gln
	His Thr	450 Ile	Phe	Dhe	цуз	361	455	met	Pro	Glu	Gly	Tyr 460	Val	Gln	Glu	Arg
25	Thr 465			- 110	цуъ	470	Asp	GIY	Asn	Tyr	Lys	Thr	Arg	Ala	Glu	Val
	Lys	Phe (3lu	Gly	Asp	Thr	Leu	Val	Asn	Ara	475	01		_		480
	_				485					490	116	GIU	ren	гуз	GLY	Ile
	Asp :	Phe 1	Lys	Glu 500	Asp	Gly	Asn	Ile	Leu 505	Gly	His	Lys	Leu	Glu	Tyr	Asn
30	Tyr 1								Met							
	Ile I	230 Jàs <i>r</i>	al i	Asn :	Phe :	Lys	Ile	Arg	His	Asn	Ile	Glu	525 Asp	Gly	Ser	Val
35	Gln I 545										Pro					
	Val L	eu L	eu I	Pro A	Asp <i>1</i> 565	Asn	His	Tyr	Leu	Ser	Thr	Gln :	Ser .	Ala	Leu	560 Ser
	Lys A	sp P	ro A	sn. (3lu I	ys .	Arg /	Asp :	His : 585	570 Met	Val 1	Leu 1	Leu (Glu	575 Phe	Val
40	Thr A	la A 5	la G 95	ly I	le 7	hr :	Leu (3ly 1 600	Met :	Asp (3lu I		ryr 1	590 Lys		
			(2)	INFO	RMAT	CION			ו מז	NO : 66	: .	•	505			
45											•					
.0		(1)	SEQ	UENC	E CH	ARAC	TER	STIC	CS:							
		(E	3) T	YPE .	n: Z	913 1656	base aci	pai	rs							
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50		(I)) T	OPOL	OGY:	lin	ear	gie								
		(ii) (ix)	MOI FE	LECU! ATUR!	LE T	YPE:	CDN	A								
55		(A) N	JAME,	KEY	: Co	ding	Seq	uenc	е						
		Ċ	D) C	THEF	S INE	: I. PORM	29 ATIO	10 N:								

(D) OTHER INFORMATION:

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

		•	•	_					_	_							
5			_	GAG Glu	_		_										48
10				GAA Glu 20													96
15				TCC Ser												_	144
.0				GAA Glu												_	192
20				GAC Asp										-			240
25				CCT Pro													288
30				GGT Gly 100											_	_	336
35				CCG Pro											_	_	384
				CTT Leu											_		432
40				ACT Thr													480
45				CTT Leu													528
50				CAC His 180													576
55				CCT Pro													624
	TTA	GCT	CCA	GAA	GTA	CAA	AGC	TCC	GAA	GAA	TAT	ATT	CAG	CTA	TTG	AAG	672

	144	
	Leu Ala Pro Glu Val Gln Ser Ser Glu Glu Tyr Ile Gln Leu Leu Lys 210 215 220	
5	AAG CTT ATT AGG TCG CCT AGC ATA CCT CAT CAG TAT TGG CTT ACG CTT Lys Leu Ile Arg Ser Pro Ser Ile Pro His Gln Tyr Trp Leu Thr Leu 230 235 240	720
10	CAG TAT TTG TTA AAA CAT TTC TTC AAG CTC TCT CAA ACC TCC AGC AAA Gln Tyr Leu Leu Lys His Phe Phe Lys Leu Ser Gln Thr Ser Ser Lys 245 250 255	768
15	AAT CTG TTG AAT GCA AGA GTA CTC TCT GAA ATT TTC AGC CCT ATG CTT Asn Leu Leu Asn Ala Arg Val Leu Ser Glu Ile Phe Ser Pro Met Leu 260 265 270	816
	TTC AGA TTC TCA GCA GCC AGC TCT GAT AAT ACT GAA AAC CTC ATA AAA Phe Arg Phe Ser Ala Ala Ser Ser Asp Asn Thr Glu Asn Leu Ile Lys 275 280 285	864
20	GTT ATA GAA ATT TTA ATC TCA ACT GAA TGG AAT GAA CGA CAG CCT GCA Val Ile Glu Ile Leu Ile Ser Thr Glu Trp Asn Glu Arg Gln Pro Ala 290 295 300	912
25	CCA GCA CTG CCT CCT AAA CCA CCA AAA CCT ACT ACT GTA GCC AAC AAC Pro Ala Leu Pro Pro Lys Pro Pro Lys Pro Thr Thr Val Ala Asn Asn 305 310 315 320	960
30	GGT ATG AAT AAC AAT ATG TCC TTA CAA AAT GCT GAA TGG TAC TGG GGA Gly Met Asn Asn Met Ser Leu Gln Asn Ala Glu Trp Tyr Trp Gly 325 330 335	1008
35	GAT ATC TCG AGG GAA GAA GTG AAT GAA AAA CTT CGA GAT ACA GCA GAC Asp Ile Ser Arg Glu Glu Val Asn Glu Lys Leu Arg Asp Thr Ala Asp 340 345 350	1056
	GGG ACC TTT TTG GTA CGA GAT GCG TCT ACT AAA ATG CAT GGT GAT TAT Gly Thr Phe Leu Val Arg Asp Ala Ser Thr Lys Met His Gly Asp Tyr 355 360 365	1104
40	ACT CTT ACA CTA AGG AAA GGG GGA AAT AAC AAA TTA ATC AAA ATA TTT Thr Leu Thr Leu Arg Lys Gly Gly Asn Asn Lys Leu Ile Lys Ile Phe 370 380	1152
45	CAT CGA GAT GGG AAA TAT GGC TTC TCT GAC CCA TTA ACC TTC AGT TCT His Arg Asp Gly Lys Tyr Gly Phe Ser Asp Pro Leu Thr Phe Ser Ser 390 395 400	1200
50	GTG GTT GAA TTA ATA AAC CAC TAC CGG AAT GAA TCT CTA GCT CAG TAT Val Val Glu Leu Ile Asn His Tyr Arg Asn Glu Ser Leu Ala Gln Tyr 405 410 415	1248
55	AAT CCC AAA TTG GAT GTG AAA TTA CTT TAT CCA GTA TCC AAA TAC CAA Asn Pro Lys Leu Asp Val Lys Leu Leu Tyr Pro Val Ser Lys Tyr Gln 420 425 430	1296
	CAG GAT CAA GTT GTC AAA GAA GAT AAT ATT GAA GCT GTA GGG AAA AAA	1344 144

										145							
	Gln	Asp	Gln 435	Val	Val	Lys	Glu	Asp 440	Asn	Ile	Glu	Ala	Val 445	Gly	Lys	Lys	
5					AAC Asn												1392
10					GAA Glu												1440
15					GAA Glu 485												1488
					CAA Gln	_							_	_		_	1536
20					AAT Asn												1584
25					TCT Ser		_				_						1632
30			_		TTG Leu										_		1680
35					AGC Ser 565	_					_	_				_	1728
					TTG Leu												1776
40					TGG Trp												1824
45					GAT Asp						~						1872
50					AGC Ser												1920
55					ACT Thr 645												1968
	TAT	GCC	TGC	TCT	GTA	GTG	GTG	GAC	GGC	GAA	GTA	AAG	CAT	TGT	GTC	ATA	2016

				16	
	Tyr Ala Cys s	Ser Val Val Val 560	Asp Gly G 665	lu Val Lys His	Cys Val Ile 670
5	675		680	CC GAG CCC TAT la Glu Pro Tyr 685	Asn Leu Tyr
10	690	695	Led His T	AC CAA CAC ACC or grant of the state of the	Ser Leu Val
15	705	710	ANT TUE TE	TA GCC TAC CCA (eu Ala Tyr Pro V 715	/al Tyr Ala 720
	CAG CAG AGG CO	GA CAG GAT CCA rg Gln Asp Pro 725	CCG GTC GC Pro Val Al 73	CC ACC ATG GTG A a Thr Met Val S	GC AAG GGC 2208 der Lys Gly 735
20	GAG GAG CTG TT Glu Glu Leu Ph 74	ie iii Giy vai	GTG CCC AT Val Pro Il 745	C CTG GTC GAG C e Leu Val Glu L 7	TG GAC GGC 2256 eu Asp Gly 50
25	GAC GTA AAC GG Asp Val Asn Gl 755	1 2 2/5 THE	AGC GTG TC Ser Val Se: 760	C GGC GAG GGC G r Gly Glu Gly G 765	AG GGC GAT 2304 lu Gly Asp
30	GCC ACC TAC GG Ala Thr Tyr Gl 770	C AAG CTG ACC (y Lys Leu Thr 1 775	CTG AAG TTO Leu Lys Phe	C ATC TGC ACC AC E lle Cys Thr Th 780	CC GGC AAG 2352 or Gly Lys
35	785	790	deu val Thr	C ACC CTG ACC TA Thr Leu Thr Ty 795	r Gly Val 800
40	CAG TGC TTC AGG Gln Cys Phe Ser	805	sp HIS Met 810	Lys Gln His As	p Phe Phe 815
40	AAG TCC GCC ATC Lys Ser Ala Met 820)	825	Glu Arg Thr Il	e Phe Phe O
45	AAG GAC GAC GGC Lys Asp Asp Gly 835	84	nr Arg Ala 40	Glu Val Lys Pho 845	e Glu Gly
50	GAC ACC CTG GTG Asp Thr Leu Val 850	AAC CGC ATC GA Asn Arg Ile GI 855	AG CTG AAG lu Leu Lys	GGC ATC GAC TTC Gly Ile Asp Phe 860	C AAG GAG 2592 Lys Glu
55	GAC GGC AAC ATC Asp Gly Asn Ile 865	CTG GGG CAC AF Leu Gly His Ly 870	AG CTG GAG	TAC AAC TAC AAC Tyr Asn Tyr Asn 875	C AGC CAC 2640 Ser His 880
	AAC GTC TAT ATC	ATG GCC GAC AA	AG CAG AAG	AAC GGC ATC AAG	GTG AAC 2688

										147							
	Asn	Val	Tyr	Ile	Met 885	Ala	Asp	Lys	Gln	Lys 890	Asn	Gly	Ile	Lys	Val 895	Asn	
5						AAC Asn											2736
10 .						ACC Thr											2784
4.5						AGC Ser											2832
15						ATG Met 950											2880
20						GAC Asp					TAA						2913
25		(i				ATION				NO : 6	57:						
30		•	(A) (B) (C)	LENG TYPI STRA	GTH: E: ar ANDEI	970 mino ONESS Y: 1:	amin acio 3: s:	no ao i ingle	cids								
35		(7	v) FI	RAGMI	ENT T	TYPI TYPE DESC	: in	terna	al	Q ID	NO:	67:					
	Met 1	Ser	Ala	Glu	Gly 5	Tyr	Gln	Tyr	Arg	Ala 10	Leu	Tyr	Asp	Tyr	Lys 15	Lys	
40		_		20	_	Ile	_		25		_	_		30			
		-	35			Val	*	40	-			_	45		,		
45		50				Pro	55					60				Gly Lvs	
	65					70 Thr					75					80	
50	Val	Ala	Pro			Ser	Lys	Thr		90 Ala	Asp	Val	Glu			Ala	
	Leu	Thr		100 Pro		Leu	Ala		105 Gln	Phe	Ala	Pro	Pro 125	110 Asp		Ala	
55	Pro	Pro	115 Leu	Leu	Ile	Lys	Leu 135	120 Val	Glu	Ala	Ile	Glu 140	Lys	Lys	Gly	Leu	
	Glu		Ser	Thr	Leu	Tyr		Thr	Gln	Ser	Ser			Leu	Ala	Glu	1.4

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5																						
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	Le	eu .	Ala	Pr	o G1	u V	al	Glı	n Se	er	Ser	G1	u (Glu	Ty	r I	le	Gla	, 1 T.e	31 T.	- 11	Lys
10																						
10	יר ה	/S . 25	Leu	110	e Ar	g s	er	Pro	S∈	er	Ile	Pr	o I	lis	G1	n Ty	r	Trp	Le	u T	hr	Leu
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20																						
	30	5	тa	Leu	Pro	Э P:	ro	Lys	Pr	o F	ro	Lys	s P	ro	Thr	Th	r V	al	Ala	a As	n.	Asn
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25																						
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30																						
					Gly																	
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35																						
	GIU	As	sp (31n 435	Val	۷a	l L	ys	Glu	As	sp .	Asn	11	е (Glu	Ala	Va	al (Gly	Lvs	s L	vs
		45	50	J_ u	Tyr	AS	11 1	nr	GIN 455	Pr	ie (Gln	Gl	u I	Lys	Ser	Ar	g	Glu	Туз	- A	sp
40					Glu																	
	Arg	Th	r A	lla	Ile	Glı	1 A	la :	Phe	As	n (3lu	Th	r J	175 17e	Lve	т٦	_ 1)ho	~1. .	4	B0
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	Lys	AL	9 9	15	GIY	ASI	1 G.	Iu]	ГÀв	G1	u I	lle	Glı	n A	rg	Ile	Мe	t H	Iis	Asn	Ty	r
	Asp																					
50	Leu 545	Gl	u G	lu 1	Asp	Leu	L	/s I	уs	G 1:	n A	la	A1:	. G	311	540 Tur	7 ~·	- 0	ı	- 1 -	_	
	Lys	Arg	g M	et A	Asn	Ser	Il	le I	ys	Pro	o A	sp	Leu	ı I	le (Gln	Lei	ı A	ra	Lvs	Th	· ·
55	Arg	****	. ف	-11 1	580	-eu	Мe	t I	rp	Let	ı T	hr	Gln	L	ys (Зlу	۷a	l A	rg	Gln	Lу	s
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	Asn		Glv	Ser	Ser	Asn		Δen	Lve	Δla	Glu		I.e.ii	T.em	Ara	Glv
5	625	Vu1	017	001	001	630	9		- 70	712.0	635	non	D Cu	Бец	nr 9	640
·		Ara	Asp	Glv	Thr		Len	Val	Ara	Glu		Ser	Live	Gln	Glv	
	~, 0		р	017	645				•••• 9	650		DC1	L, J	0111	655	Cys
	Tvr	Ala	Cvs	Ser	Val	Val	Val	αsA	Glv		Val	Lvs	His	Cvs		Tle
	-1-		-1-	660					665			-7-		670		
10	Asn	Lvs	Thr		Thr	Glv	Tvr	Glv		Ala	Glu	Pro	Tvr		Leu	Tvr
		-	675			•	•	680					685			-
	Ser	Ser	Leu	Lys	Glu	Leu	Val	Leu	His	Tyr	Gln	His	Thr	Ser	Leu	Val
		690		-			695			•		700				
	Gln	His	Asn	Asp	Ser	Leu	Asn	Val	Thr	Leu	Ala	Tyr	Pro	Val	Tyr	Ala
15	705					710					715	_			_	720
	Gln	Gln	Arg	Arg	Gln	Asp	Pro	Pro	Val	Ala	Thr	Met	Val	Ser	Lys	Gly
					725					730				•	735	
	Glu	Glu	Leu	Phe	Thr	Gly	Val	Val	Pro	Ile	Leu	Val	Glu	Leu	Asp	Gly
				740					745					750		
20	Asp	Val	Asn	Gly	His	Lys	Phe	Ser	Val	Ser	Gly	${\tt Glu}$	Gly	Glu	Gly	Asp
			755					760					765			
	Ala	Thr	Tyr	Gly	Lys	Leu	Thr	Leu	Lys	Phe	Ile	Cys	Thr	Thr	Gly	Lys
		770					775					780				
		Pro	Val	Pro	Trp		Thr	Leu	Val	Thr		Leu	Thr	Tyr	Gly	Val
25	785					790					795					800
	Gln	Cys	Phe	Ser	Arg	Tyr	Pro	Asp	His		-	Gln	His	Asp		Phe
					805					810				_	815	
	Lys	Ser	Ala		Pro	Glu	GIY	Tyr		Gln	Glu	Arg	Thr		Phe	Phe
20	_	_		820	_	_		_,	825				_	830		
30	гуѕ	Asp		сту	Asn	Tyr	гуѕ		Arg	Ата	GIU	vaı	_	Pne	GIU	GIY
	7 an	Thr	835	V-1	Asn	7.~~	T10	840	τ	7	~ 1	T1 -	845	Dha	T	C1
	мвр	850	Leu	val	ASII	Arg	855	Gru	ьец	пЛR	GIA	860	Asp	Pne	гуя	GIU
	Aen		Δen	Tle	Leu	Glv		Lve	ī.eu	Glu	Tur		Tur	Δen	Ser	Hic
35	865	017	11511		ДСС	870	*****	дув	Deu	Olu	875	Hom	1 y 1	Abii	JCI	880
		Val	Tvr	Tle	Met		Asp	Lvs	Gln	Lvs		Glv	Tle	Lvs	Val	
			-3-		885			-1-		890		017		_,_	895	
	Phe	Lys	Ile	Arq	His	Asn	Ile	Glu	Asp		Ser	Val	Gln	Leu	_	Asp
		•		900					905	2.				910		
40	His	Tyr	Gln	Gln	Asn	Thr	Pro	Ile	Gly	Asp	Gly	Pro	Val	Leu	Leu	Pro
			915					920	-	-	-		925			
	Asp	Asn	His	Tyr	Leu	Ser	Thr	Gln	Ser	Ala	Leu	Ser	Lys	Asp	Pro	Asn
		930					935					940				
	Glu	Lys	Arg	Asp	His	Met	Val	Leu	Leu	${\tt Glu}$	Phe	Val	Thr	Ala	Ala	Gly
45	945					950					955					960
	Ile	Thr	Leu	Gly	Met	Asp	Glu	Leu	Tyr	Lys						
					965					970						
						•										
50			(2)	INI	FORM	OITA	1 FOI	SEC) ID	NO: 6	58:					
50																

(i) SPOITENCE CUA

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 1788 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
- 55 (D) TOPOLOGY: linear

150

(ii) MOLECULE TYPE: cDNA (ix) FEATURE:

(A) NAME/KEY: Coding Sequence (B) LOCATION: 1...1785 5

(D) OTHER INFORMATION:

10 ATG GGC AAC GCC GCC GCC GCC AAA AAA GGC AAG CAG C				(xi)	SEC	QUENC	E DE	SCRI	PTIC	ON: S	EQ 1	D NO	0:68	:					
20 25 Ala May Pine Leu Lys Lys Trp Glu 30 25 Ala May Pine Leu Lys Lys Trp Glu 310 30 Asp Pro Ser Gln Ash The Ala Gln Leu Asp Gln Pine Asp Arg Ile Lys 45 Asp Pro Ser Gln Ash The Ala Gln Leu Asp Gln Pine Asp Arg Ile Lys 40 45 Asp Pro Ser Gln Ash The Ala Gln Leu Asp Gln Pine Asp Arg Ile Lys 40 Asp Pro Ser Gln Ash The Ala Gln Leu Asp Gln Pine Asp Arg Ile Lys 40 Asp Pro Ser Pine Gly Arg Val Met Leu Val Lys His Lys 10 10 10 10 10 10 10 10 10 10 10 10 10	10	1				5	u AI	a Al	ашу	с гу	10 s G1	у Ѕе	er G	lu G	ln G	lu S 1	er 5	Val	48
ACC CTT GGC ACC GGC TCC TTT GGG CGA GTG ATG CTG GTG AAG CAC AAG Thr Leu Gly Thr Gly Ser Phe Gly Arg Val Met Leu Val Lys His Lys 50 GAG AGT GGG AAC CAC TAC GCC ATG AAG ATG TTA GAC AAG CAG AAG GTG Glu Ser Gly Asn His Tyr Ala Met Lys Ile Leu Asp Lys Gln Lys Val 65 GTG AAG CTA AAG CAG ATC GAG CAC ACT CTG AAT GAG AAG CGC ATC CTG 85 CAG GCC GTC AAC TTC CCG TTC CTG GTC AAA CTT GAA AAG CAG AAG CTG Val Lys Leu Lys Gln Ile Glu His Thr Leu Asn Glu Lys Arg Ile Leu 85 CAG GCC GTC AAC TTC CCG TTC CTG GTC AAA CTT GAA TTC TCC TTC AAG Gln Ala Val Asn Phe Pro Phe Leu Val Lys Leu Glu Phe Ser Phe Lys 100 GAC AAC TCA AAC CTG TAC ATG GTC ATG GAG TAT GTA GTA GCT GGT GGC GAG Asp Asn Ser Asn Leu Tyr Met Val Met Glu Tyr Val Ala Gly Gly Glu 115 ATG TTC TCC CAC CTA CGG CGG ATT GGA AGG TTC ACC GAG CCC CAT GCC Met Phe Ser His Leu Arg Arg Ile Gly Arg Phe Ser Glu Pro His Ala 130 ATG TTC TCC CAC CTA CGG GG ATT GGA AGG TTC ACC GAG CCC CAT GCC Met Phe Ser His Leu Arg Arg Ile Gly Arg Phe Ser Glu Pro His Ala 130 CGT TTC TAC GCG GG CAG ATC GTC CTG AAC CTT GAG TTC TCC ACC TCC Arg Phe Tyr Ala Ala Gli Ile Val Leu Thr Phe Glu Tyr Leu His Ser 140 CGT TTC TAC GCG GG CAG ATC GTC CTG AAC CTT GAG TTC CAC TCC Arg Phe Tyr Ala Ala Gli Ile Val Leu Thr Phe Glu Tyr Leu His Ser 145 CAG CAG CAC CTC ATC TAC CGG GAC CTG AAG CCC GAG AAT CTT CTC ATC GAC Leu Asp Leu Ile Tyr Arg Asp Leu Lys Pro Glu Asn Leu Leu Ile Asp 165 CAG CAG CAG GCC TAT ATT CAG GTG ACA GAC TTC GGT TTT GCC AAC CTT GAC Glu Asn Leu Leu Ile Asp 165 CAG CAG CAG GCC TAT ATT CAG GTG ACA GAC TTC GGT TTT GCC AAG CCT GTG Gln Gln Gln Gly Tyr Ile Gln Val Thr Asp Phe Gly Phe Ala Lys Arg Val	15	_			20		ч шу	o AI	а гу	25	u As	p Ph	e Le	eu Ly	/s Ly 3(/s T)	rp	Glu	96
25	20	-		35			1111	r MI	40	n re	u As _i	p G1	n Ph	1e As 45	p Ar	gI	le	Lys	144
65 70 70 80 175 180 180 175 180 180 175 80 180 281 281 281 281 281 281 281 281 281 281	25		50	•			501	55	e GI	y Arg	y va.	L Me	t Le 60	u Va	1 Ly	s H	is	Lys	192
CAG GCC GTC AAC TTC CCG TTC CTG GTC AAA CTT GAA TTC TCC TTC AAG AAG AAA CTT GAA TTC TCC TTC AAG AAG AAA CTT AAT AAT AAA CTT GAA TTC TCC AAA GAA AAA CTT GAA TTC TCC AAA AAA AAA AAA AAA AAA AAA A	20	65		-	•		70	7110	net	. цув	116	75	ı As	р Гу	s Gl	n L	/S	Val 80	240
GAC AAC TCA AAC CTG TAC ATG GTC ATG GAG TTC AGC GAG GAG CCC CAT GCC ATG GAG ASP	30		•		_,_	85	116	GIU	nis	inr	90	Asn	ı Glı	u Lys	s Ar	9 I I 95	e	Leu	288
ATG TTC TCC CAC CTA CGG CGG ATT GGA AGG TTC AGC GAG CCC CAT GCC 432 Met Phe Ser His Leu Arg Arg Ile Gly Arg Phe Ser Glu Pro His Ala 130 CGT TTC TAC GCG GCG CAG ATC GTC CTG ACC TTT GAG TAT CTG CAC TCC Arg Phe Tyr Ala Ala Gln Ile Val Leu Thr Phe Glu Tyr Leu His Ser 150 CTG GAC CTC ATC TAC CGG GAC CTG AAG CCC GAG AAT CTT CTG CAC TCC ATC GAC Leu Asp Leu Ile Tyr Arg Asp Leu Lys Pro Glu Asn Leu Leu Ile Asp 165 CAG CAG GGC TAT ATT CAG GTG ACA GAC TTC GGT TTT GCC AAG CGT GTG 576 GIn Gln Gly Tyr Ile Gln Val Thr Asp Phe Gly Phe Ala Lys Arg Val	35				100	2110	110	FILE	Leu	105	гуs	Leu	Glu	ı Phe	Ser 110	Ph	e :	Lys	336
130 CGT TTC TAC GCG GCG CAG ATC GTC CTG ACC TTT GAG TAT CTG CAC TCC ARG Phe Tyr Ala Ala Ala Gln Ile Val Leu Thr Phe Glu Tyr Leu His Ser 160 CTG GAC CTC ATC TAC CGG GAC CTG AAG CCC GAG AAT CTT CTC ATC GAC Leu Asp Leu Ile Tyr Arg Asp Leu Lys Pro Glu Asn Leu Leu Ile Asp 165 CAG CAG GGC TAT ATT CAG GTG ACA GAC TTC GGT TTT GCC AAG CGT GTG 576 Gln Gln Gly Tyr Ile Gln Val Thr Asp Phe Gly Phe Ala Lys Arg Val	40			115			- 7 -	Mec	120	Met	Glu	Tyr	Val	Ala 125	Gly	Gl;	у (Glu	384
145 150 150 155 160 CTG GAC CTC ATC TAC CGG GAC CTG AAG CCC GAG AAT CTT CTC ATC GAC Leu Asp Leu Ile Tyr Arg Asp Leu Lys Pro Glu Asn Leu Leu Ile Asp 165 170 175 CAG CAG GGC TAT ATT CAG GTG ACA GAC TTC GGT TTT GCC AAG CGT GTG 576 Gln Gln Gly Tyr Ile Gln Val Thr Asp Phe Gly Phe Ala Lys Arg Val	45		130				9	135	116	GIA	Arg	Phe	Ser 140	Glu	Pro	His	s P	Ala	432
Leu Asp Leu Ile Tyr Arg Asp Leu Lys Pro Glu Asn Leu Leu Ile Asp 165 170 175 CAG CAG GGC TAT ATT CAG GTG ACA GAC TTC GGT TTT GCC AAG CGT GTG 576 Gln Gln Gly Tyr Ile Gln Val Thr Asp Phe Gly Phe Ala Lys Arg Val		CGT Arg	TTC Phe	TAC Tyr	GCG Ala		0111	ATC Ile	GTC Val	CTG Leu	ACC Thr	Phe	GAG Glu	TAT Tyr	CTG Leu	CAC	S	er	480
180 The Asp Phe Gly Phe Ala Lys Arg Val	50	CTG (GAC Asp	CTC Leu	ATC Ile	- ,	CGG Arg .	GAC Asp	CTG Leu	AAG Lys	Pro	GAG Glu	AAT Asn	CTT Leu	CTC Leu	Ile	A	AC sp	528
	55	CAG (CAG (GGC Gly	TAT Tyr 180	ATT (CAG (GTG . Val	IIII.	Asp	TTC	GGT Gly	TTT Phe	GCC Ala	Lys	CGT Arg	V:	TG al	576

_			ACT Thr								624
5			CTG Leu								672
10			CTC Leu								720
15		•	CCT Pro								768
20			TCC Ser 260								816
25			GTG Val								864
			ATC Ile								912
30			CAG Gln								960
35	_	_	GAC Asp						_	_	1008
40			ATC Ile 340								1056
45			AGT Ser								1104
.0			TTA Leu								1152
50			GAA Glu								1200
55			ACT Thr								1248

152

AAA CAG CAT GAC TIT TIC AAG AGT GCC ATG CCC GAA GGT TAT GTA CAG Lys Gin His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gin 435 10 GAA AGA ACT ATA TIT TAC AAA GAT GAC GGG AAC TAC AAG ACA CGT GCT GIU Arg Thr 11e Phe Tyr Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala 450 450 GAA GAC ACT ATA TIT TAC AAA GAT GAC GGG AAC TAC AAG ACA CGT GCT 450 GAA GTC AAG TIT GAA GGT GAT ACC CTT GTT AAT AGA ATC GAG TTA AAA 610 Val Lys Phe Glu Gly Asp Thr Leu Val Ash Arg Ile Glu Leu Lys 465 GGT ATT GAT TIT AAA GAA GAT GGA AAC ATT CTT GGA CAC AAA ATG GAA 61y 1le Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Met Glu 485 TAC AAT TAT AAC TCA CAT AAT GTA TAC ATC ATG GCA GAC AAA ACC AAG Tyr Asn Tyr Asn Ser His Asn Val Tyr 1le Met Ala Asp Lys Pro Lys 500 505 AAT GGC ATC AAA GTT AAC TCA AAA ATT AGA CAC AAC AATA ASP GLY ASP Gly Asn Gly 1le Lys Val Asn Phe Lys 1le Arg His Asn 1le Lys Asp Gly 515 AAT GGC ATC CAT TAC TAC ATA ATT CAA CAA AAT ACT CCA ATT GAG GAT ASP Gly Ile Lys Val Asn Phe Lys 1le Arg His Asn 1le Lys Asp Gly 515 ACC GTT CAA TTA GCA GAC CAT TAT CAA CAA AAT ACT CCA ATT GAG GAT Ser Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp 530 ACC GTT CAA TTA CCA GAC AAC CAT TAC CTG TCC ACG CAA TCT GCC Gly Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala 550 GCC CCT GTC CTT TTA CCA GAC AAA AGA GAT CAC ATG ATG ATG ATG ATG Gly Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala 550 CTT TCC AAA GAT CCC AAC GAA AAG AAG AGA CAT GAT GAT CTC TCT GAC ACT CTG GAG GAT AAC GAS AAG AAG AGA CAT GAT GAT CTC TCT GAC ACT CAT GAC GCG GAG ATT ACA CAT GCC ATG GAT GAA CTA TAC ATA GAT GAT GAC ATG ATG GAT GAA CCT CAG GAG TAA Pro Gln Glu 550 (2) INFORMATION FOR SEO ID NO:69: (1) INFORMATION FOR SEO ID NO:69:	5	ACT CTC ACT TAT GGT GTT CAA TGC TTT TCT AGA TAC CCA GAT CAT ATG Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met 420 425 430	1296
450 455 455 455 456 457 458 459 455 466 GAA GTC AAG TTT GAA GGT GAT ACC CTT GTT AAT AGA ATC GAG TTA AAA GLU Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys 465 GGT ATT GAT TTT AAA GAA GAT GGA AAC ATT CTT GGA CAC AAA ATG GAA GLy Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Met Glu 485 TAC AAT TAT AAC TCA CAT AAT GTA TAC ATC ATG GCA GAC AAA CCA AAG Tyr Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Pro Lys 500 AAT GGC ATC AAA GTT AAC TTC AAA ATT AGA CAC AAC ATT AAA GAT GGA Asn Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Lys Asp Gly 515 AAT GGC ATC AAA GTT AAC TTC AAA ATT AGA CAC AAC ATT AAA GAT GGA Asn Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Lys Asp Gly 515 GGC CTT CAA TTA GCA GAC CAT TAT CAA CAA AAT ACT CCA ATT GGC GAT Ser Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp 530 GGC CCT GTC CTT TTA CCA GAC AAC CAT TAC CTG TCC ACG CAA TCT GCC 356 GGP Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala 550 CTT TCC AAA GAT CCC AAC GAA AAG AAG AAG AAC CAT TAC CTG TCC ACG CAA TCT GCC 460 CTT TCC AAA GAT CCC AAC GAA AAG AGA GAT CAC ATG ATC CTT CTT GAG Leu Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Ile Leu Leu Glu 566 CTT TCC AAA GAT CCC GGG ATT ACA CAT GGC ATG GAT GAA CTA TAC AAA Phe Val Thr Ala Ala Gly Ile Thr His Gly Met Asp Glu Leu Tyr Lys 580 CCT CAG GAG TAA Pro Gln Glu 595 (2) INFORMATION FOR SEQ ID NO:69: (1) SEQUENCE CHARACTERISTICS.		435 440 Glu Gly Tyr Val Gln	1344
465 470 475 480 475 480 GGT ATT GAT TIT AAA GAA GAT GGA AAC ATT CTT GGA CAC AAA ATG GAA GIV Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Met Glu 490 TAC AAT TAT AAC TCA CAT AAT GTA TAC ATC ATG GCA GAC AAA CCA AAG TYR ASN TYR ASN Ser His ASN Val Tyr Ile Met Ala Asp Lys Pro Lys 500 501 AAT GGC ATC AAA GTT AAC TTC AAA ATT AGA CAC AAC ATT AAA GAT GGA ASN Gly Ile Lys Val ASN Phe Lys Ile Arg His ASN Lys Pro Lys 510 AAT GGC ATC CAT TA GCA GAC CAT TAT CAA ATT AGA CAC AAC ATT AAA GAT GGA ASN Gly Ile Lys Val ASN Phe Lys Ile Arg His ASN Thr Pro Ile Gly Asp Gly 515 GGC GTT CAA TTA GCA GAC CAT TAT CAA CAA AAT ACT CCA ATT GGC GAT Ser Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp 530 GGC CCT GTC CTT TTA CCA GAC AAC CAT TAC CTG TCC ACG CAA TCT GCC Gly Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala 560 CTT TCC AAA GAT CCC AAC GAA AAG AGA GAT CAC ATG ATC CTT CTT GAG 1728 Leu Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Ile Leu Leu Glu 570 TTT GTA ACA GCT GCT GGG ATT ACA CAT GGC ATT GAT GAA CTA TAC AAA PRO Glu Leu Tyr Lys 580 CCT CAG GAG TAA Pro Gln Glu 595 (1) Information for Seo ID No:69:	10	450 Asp Asp Gly Asn Tyr Lys Thr Arg Ala 455 460	1392
20 485 485 486 490 490 495 495 TAC AAT TAT AAC TCA CAT AAT GTA TAC ATC ATG GCA GAC AAA CCA AAG TYT ASN TYT ASN SET HIS ASN VAI TYT ILE MET ALA ASD LYS PTO LYS 500 505 AAT GGC ATC AAA GTT AAC TTC AAA ATT AGÀ CAC AAC ATT AAA GAT GGA ASN GIY ILE Lys Val ASN PHE Lys ILE ATG HIS ASN ILE LYS ASP GIY 515 30 AGC GTT CAA TTA GCA GAC CAT TAT CAA CAA AAT ACT CCA ATT GGC GAT SET VAI GIN LEU ALA ASP HIS TYT GIN GIN ASN THE PTO ILE GIY ASP 530 GGC CCT GTC CTT TTA CCA GAC AAC CAT TAC CTC ACG CAA TCT GCC GIY PTO VAI LEU LEU PTO ASP ASN HIS TYT LEU SET THT GIN SET ALA 545 CCTT TCC AAA GAT CCC AAC GAA AAG AGA GAT CAC ATG ATC CTT CTT GAG LEU SET LYS ASP PTO ASN GIU LYS ATG ASP HIS MET ILE LEU LEU GIU 565 TTT GTA ACA GCT GCT GGG ATT ACA CAT GGC ATG GAT CAC CTT TAC AAA Phe Val Thr Ala Ala Gly Ile Thr His Gly Met Asp Glu Leu Tyr Lys 580 CCT CAG GAG TAA PTO GIN GIU 595 (2) INFORMATION FOR SEQ ID NO:69:	15	465 470 475 480	1440
25 AAT GGC ATC AAA GTT AAC TTC AAA ATT AGA CAC AAC ATT AAA GAT GGA ASD GIY IIe Lys Val Asn Phe Lys 515 30 AGC GTT CAA TTA GCA GAC CAT TAT CAA CAA AAT ACT CCA ATT GGC GAT S30 Ser Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro IIe Gly Asp 530 35 GGC CCT GTC CTT TTA CCA GAC AAC CAT TAC CTG TCC ACG CAA TCT GCC Gly Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala 550 CTT TCC AAA GAT CCC AAC GAA AAG AGA GAT CAC ATG ATC CTT CTG GAC Leu Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met IIe Leu Leu Glu 570 TTT GTA ACA GCT GCT GGG ATT ACA CAT GGC ATG GAT GAA CTA TAC AAA Phe Val Thr Ala Ala Gly IIe Thr His Gly Met Asp Glu Leu Tyr Lys 580 CCT CAG GAG TAA Pro Gln Glu 595 (2) INFORMATION FOR SEQ ID NO:69:	20	485 490 495	1488
30 AGC GTT CAA TTA GCA GAC CAT TAT CAA CAA AAT ACT CCA ATT GGC GAT 530 535 The Arg His Asn Thr Pro Ile Gly Asp 530 540 35 GGC CCT GTC CTT TTA CCA GAC AAC CAT TAC CTG TCC ACG CAA TCT GCC 1680 550 550 550 550 550 550 550 550 550 5	25	500 505 FIGURE AND LYS Pro Lys	1536
S30 S35 S35 S40 S40		515 The Bys Tie Arg His Asn Ile Lys Asp Gly 525	1584
545 CTT TCC AAA GAT CCC AAC GAA AAG AGA GAT CAC ATG ATC CTT CTT GAG 1728 Leu Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Ile Leu Leu Glu 570 TTT GTA ACA GCT GCT GGG ATT ACA CAT GGC ATG GAT GAA CTA TAC AAA 1776 Phe Val Thr Ala Ala Gly Ile Thr His Gly Met Asp Glu Leu Tyr Lys 580 CCT CAG GAG TAA Pro Gln Glu 595 (2) INFORMATION FOR SEQ ID NO:69:	30	530 535 540	1632
40 565 TTT GTA ACA GCT GCT GGG ATT ACA CAT GGC ATG GAT GAA CTA TAC AAA Phe Val Thr Ala Ala Gly Ile Thr His Gly Met Asp Glu Leu Tyr Lys 580 CCT CAG GAG TAA Pro Gln Glu 595 (2) INFORMATION FOR SEQ ID NO:69: (i) SEQUENCE CHARACTERISTICS:	35	545 550 FFF Leu Ser Thr Gln Ser Ala	1680
580 585 590 CCT CAG GAG TAA Pro Gln Glu 595 (2) INFORMATION FOR SEQ ID NO:69: (i) SEQUENCE CHARACTERISTICS:	40	565 Arg Asp His Met Ile Leu Leu Glu 575	1728
Pro Gln Glu 595 (2) INFORMATION FOR SEQ ID NO:69: (i) SEQUENCE CHARACTERISTICS:	45	580 585	1776
(2) INFORMATION FOR SEQ ID NO:69: (i) SEQUENCE CHARACTERISTICS:	·	Pro Gln Glu	1788
(i) SEQUENCE CHARACTERISTICS:	50	(0)	
(i) SEQUENCE CHARACTERISTICS:			
IAI DENGTH: 50E amin		(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 595 amino acids	

(A) LENGTH: 595 amino acids

(B) TYPE: amino acid
(C) STRANDEDNESS: single

153

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(v) FRAGMENT TYPE: internal

5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:69:

	1	_			Ala 5			_	_	10					15	
10				20	Ala				25					30		
			35		Asn			40					45			
15		5 0	_		Gly		55	-	_			60		•		-
	65				His	70					75					80
20					Gln 85					90					95	
20				100	Phe Leu				105					110		
			115		Leu			120					125			
25		130			Ala	_	135		_	_		140				
	145				Tyr	150					155					160
30					165 Ile		_		_	170					175	_
				180	Trp				185					190		
	Glu	Ile	195 Ile	Leu	Ser	Lys	Gly	200 Tyr	Asn	Lys	Ala	Val	205 Asp	Trp	Trp	Ala
35	Leu	210 Gly	Val	Leu	Ile	Tyr	215 Glu	Met	Ala	Ala	Gly	220 Tyr	Pro	Pro	Phe	Phe
	225 Ala	Asp	Gln	Pro	Ile	230 Gln	Ile	Tyr	Glu	Lys	235 Ile	Val	Ser	Gly	Lys	240 Val
40	Arg	Phe	Pro	Ser	245 His	Phe	Ser	Ser	Asp	250 Leu	Lys	Asp	Leu	Leu	255 Arg	Asn
	Leu	Leu		260 Val	Asp	Leu	Thr		265 Arg	Phe	Gly	Asn		270 Lys	Asp	Gly
45	Val		275 Asp	Ile	Lys	Asn		280 Lys	Trp	Phe	Ala		285 Thr	Asp	Trp	Ile
45	Ala 305	290 Ile	Tyr	Gln	Arg		295 Val	Glu	Ala	Pro		300 Ile	Pro	Lys	Phe	
		Pro	Gly	Asp	Thr	310 Ser	Asn	Phe	Asp	Asp	315 Tyr	Glu	Glu	Glu	Glu 335	320 Ile
50	Arg	Val	Ser	Ile 340	Asn	Glu	Lys	Cys	Gly 345		Glu	Phe	Thr	Glu 350		Gly
	Arg	Ala	Met 355		Lys	Gly	Glu	Glu 360		Phe	Thr	Gly	Val 365		Pro	Ile
55	Leu	Val 370	Glu	Leu	Asp	Gly	Asp 375		Asn	Gly	Gln	Lys		Ser	Val	Ser
	Gly	Glu	Gly	Glu	Gly	Asp		Thr	Tyr	Gly	Lys	Leu	Thr	Leu	Lys	Phe

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(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 2181 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: cDNA (ix) FEATURE: (A) NAME/KEY: Coding Sequence (B) LOCATION: 12178 (D) OTHER INFORMATION: (xi) SEQUENCE DESCRIPTION: SEQ ID NO:70: ATG AGC GAC GTG GCT ATT GTG AAG GAG GGT TGG CTG CAC AAA CGA GGG ABC Met Ser Asp Val Ala Ile Val Lys Glu Gly Trp Leu His Lys Arg Gly 15 GAG TAC ATC AAG ACC TGG CGG CCA CGC TAC TTC CTC CTC AAG AAT GAT GAT Glu Tyr Ile Lys Thr Trp Arg Pro Arg Tyr Phe Leu Leu Lys Asn Asp 20 GGC ACC TTC ATT GGC TAC AAG GAG CGG CCG CAG GAT GTG GAC CAA CGT 144 5 Gly Thr Phe Ile Gly Tyr Lys Glu Arg Pro Gln Asp Val Asp Gln Arg	^^			(2)	INF	ORMA?	rion	FOR	SEO	TD 1	NO · 7	٦.						
(A) LENGTH: 2181 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: cDNA (ix) FEATURE: 40 (A) NAME/KEY: Coding Sequence (B) LOCATION: 12178 (D) OTHER INFORMATION: (xi) SEQUENCE DESCRIPTION: SEQ ID NO:70: ATG AGC GAC GTG GCT ATT GTG AAG GAG GGT TGG CTG CAC AAA CGA GGG Met Ser Asp Val Ala Ile Val Lys Glu Gly Trp Leu His Lys Arg Gly 1 5 GAG TAC ATC AAG ACC TGG CGG CCA CGC TAC TTC CTC CTC AAG AAT GAT 96 Glu Tyr Ile Lys Thr Trp Arg Pro Arg Tyr Phe Leu Leu Lys Asn Asp 20 25 GGC ACC TTC ATT GGC TAC AAG GAG CGG CCG CAG GAT GTG GAC CAA CGT 144 55 Gly Thr Phe Ile Gly Tyr Lys Glu Arg Pro Gln Asp Val Asp Gln Arg	30								2			<i>.</i>						
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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:70: ATG AGC GAC GTG GCT ATT GTG AAG GAG GGT TGG CTG CAC AAA CGA GGG AGC ACC TTC ATC AAG ACC TGG CGG CCA CGC TAC TTC CTC CTC AAG AAT GAT GAT GGU Tyr Ile Lys Thr Trp Arg Pro Arg Tyr Phe Leu Leu Lys Asn Asp 20 25 30 GGC ACC TTC ATT GGC TAC AAG GAG CGG CCG CAG GAT GTG GAC CAA CGT 144 GGLy Thr Phe Ile Gly Tyr Lys Glu Arg Pro Gln Asp Val Asp Gln Arg				(B)	LOCA	TION	: 1.	21	78		-							
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GGC ACC TTC ATT GGC TAC AAG GAG CGG CCG CAG GAT GTG GAC CAA CGT 55 Gly Thr Phe Ile Gly Tyr Lys Glu Arg Pro Gln Asp Val Asp Gln Arg					•	-				10	D						-	
GGC ACC TTC ATT GGC TAC AAG GAG CGG CCG CAG GAT GTG GAC CAA CGT 55 Gly Thr Phe Ile Gly Tyr Lys Glu Arg Pro Gln Asp Val Asp Gln Arg	50	GAG TAG	י הי	רר אי	N.C. 3.													
GGC ACC TTC ATT GGC TAC AAG GAG CGG CCG CAG GAT GTG GAC CAA CGT 55 Gly Thr Phe Ile Gly Tyr Lys Glu Arg Pro Gln Asp Val Asp Gln Arg		Clar m	- A1	L AF	AC AC	C TG	G CC	G CC	CA CC	C T	AC TI	C CT	ים מיד	'C' 2	ימ א	ים חב	۱۳	
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GGC ACC TTC ATT GGC TAC AAG GAG CGG CCG CAG GAT GTG GAC CAA CGT 55 Gly Thr Phe Ile Gly Tyr Lys Glu Arg Pro Gln Asp Val Asp Gln Arg				20)				2	-	- PI	re re	n re	u Ly	s As	sn As	q	
35 And Arg Pro Gin Asp Val Asp Gln Arg									2.	,				30)			
35 An Arg Pro Gin Asp Val Asp Gln Arg		GGC ACC	ייים י	יר איי	TT			_										
35 And Arg Pro Gin Asp Val Asp Gln Arg	55	Gly mb-	- TT	- AI	I GG	C TA	C AA	G GA	G CG	G CC	G CA	G GA	T GT	G GA	ר כא	A CC	·m	
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5			AAC Asn		_				192
Ū			CGG Arg						240
10			GAA Glu 85						288
15			ACC Thr						336
20			GAG Glu						384
25			GAG Glu						432
			GAG Glu						480
30			ATC Ile 165						·528
35			CTC Leu						576
40			ACC Thr						624
45			CTG Leu						672
			TAC Tyr						720
50			TTC Phe 245						768
55			CTG Leu						816

5		280	Asp Lys Asp Gly His Ile 285	864
	AAG ATC ACA GAC TTC GGG CTG Lys Ile Thr Asp Phe Gly Leu 290 295	TGC AAG GAG G Cys Lys Glu G	GG ATC AAG GAC GGT GCC ly Ile Lys Asp Gly Ala 300	912
10	ACC ATG AAG ACC TTT TGC GGC Thr Met Lys Thr Phe Cys Gly 305	THE PRO GIU T)	AC CTG GCC CCC GAG GTG yr Leu Ala Pro Glu Val 15 320	960
15	CTG GAG GAC AAT GAC TAC GGC (Leu Glu Asp Asn Asp Tyr Gly 7 325	330	sp Trp Trp Gly Leu Gly 335	1008
20	GTG GTC ATG TAC GAG ATG ATG TVal Val Met Tyr Glu Met Met C	ys Gly Arg Le 345	eu Pro Phe Tyr Asn Gln 350	1056
25		60	t Glu Glu Ile Arg Phe 365	1104
	CCG CGC ACG CTT GGT CCC GAG G Pro Arg Thr Leu Gly Pro Glu A 370	ra nys ser net	u Leu Ser Gly Leu Leu 380	1152
30	AAG AAG GAC CCC AAG CAG AGG C Lys Lys Asp Pro Lys Gln Arg Lo 385	TT GGC GGG GGC eu Ġly Gly Gly 395	y Ser Glu Asp Ala Lys	1200
35	GAG ATC ATG CAG CAT CGC TTC TT Glu Ile Met Gln His Arg Phe Ph 405	TT GCC GGT ATC e Ala Gly Ile 410	C GTG TGG CAG CAC GTG Val Trp Gln His Val 415	1248
40	TAC GAG AAG AAG CTC AGC CCA CC Tyr Glu Lys Lys Leu Ser Pro Pr 420	425	Gln Val Thr Ser Glu 430	1296
45	ACT GAC ACC AGG TAT TTT GAT GAT Thr Asp Thr Arg Tyr Phe Asp Gl 435	u Giu Phe Thr	GCC CAG ATG ATC ACC Ala Gln Met Ile Thr 445	1344
	ATC ACA CCA CCT GAC CAA GAT GA Ile Thr Pro Pro Asp Gln Asp Asp 450	C AGC ATG GAG P Ser Met Glu	TGT GTG GAC AGC GAG Cys Val Asp Ser Glu 460	1392
50	CGC AGG CCC CAC TTC CCC CAG TTC Arg Arg Pro His Phe Pro Gln Phe 465	C TCC TAC TCG Ser Tyr Ser 475	GCC AGC AGC ACG GCC Ala Ser Ser Thr Ala 480	1440
55	TCG GAT CCA CCG GTC GCC ACC ATC Ser Asp Pro Pro Val Ala Thr Met 485	GTG AGC AAG Val Ser Lys 490		1488

157

5	 	GTG Val 500					_		_	1536
5		AGC Ser								1584
10		CTG Leu								1632
15	 -	CTC Leu								1680
20		GAC Asp						_		1728
25		TAC Tyr 580								1776
		ACC Thr							_	1824
30		GAG Glu								1872
35		AAG Lys					_			1920
40		AAG Lys						_		1968
45		GAG Glu 660								2016
40		ATC Ile						_		2064
50		CAG Gln								2112
55		CTG Leu								2160

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ATG GAC GAG CTG TAC AAG TAA
        Met Asp Glu Leu Tyr Lys
                                                                          2181
   5
                 (2) INFORMATION FOR SEQ ID NO:71:
              (i) SEQUENCE CHARACTERISTICS:
  10
                (A) LENGTH: 726 amino acids
                (B) TYPE: amino acid
                (C) STRANDEDNESS: single
                (D) TOPOLOGY: linear
  15
             (ii) MOLECULE TYPE: protein
             (v) FRAGMENT TYPE: internal
             (xi) SEQUENCE DESCRIPTION: SEQ ID NO:71:
  20
       Met Ser Asp Val Ala Ile Val Lys Glu Gly Trp Leu His Lys Arg Gly
       Glu Tyr Ile Lys Thr Trp Arg Pro Arg Tyr Phe Leu Leu Lys Asn Asp
                              25
       Gly Thr Phe Ile Gly Tyr Lys Glu Arg Pro Gln Asp Val Asp Gln Arg
 25
       Glu Ala Pro Leu Asn Asn Phe Ser Val Ala Gln Cys Gln Leu Met Lys
                             55
       Thr Glu Arg Pro Arg Pro Asn Thr Phe Ile Ile Arg Cys Leu Gln Trp
      Thr Thr Val Ile Glu Arg Thr Phe His Val Glu Thr Pro Glu Glu Arg
                                            75
 30
                    85
                                         90
      Glu Glu Trp Thr Thr Ala Ile Gln Thr Val Ala Asp Gly Leu Lys Lys
                                    105
      Gln Glu Glu Glu Met Asp Phe Arg Ser Gly Ser Pro Ser Asp Asn
 35
                                 120
      Ser Gly Ala Glu Glu Met Glu Val Ser Leu Ala Lys Pro Lys His Arg
                             135
                                         140
      Val Thr Met Asn Glu Phe Glu Tyr Leu Lys Leu Leu Gly Lys Gly Thr
                        150
      Phe Gly Lys Val Ile Leu Val Lys Glu Lys Ala Thr Gly Arg Tyr Tyr
40
                     165
                                        170
      Ala Met Lys Ile Leu Lys Lys Glu Val Ile Val Ala Lys Asp Glu Val
                                    185
      Ala His Thr Leu Thr Glu Asn Arg Val Leu Gln Asn Ser Arg His Pro
45
                              200
      Phe Leu Thr Ala Leu Lys Tyr Ser Phe Gln Thr His Asp Arg Leu Cys
                     215
      Phe Val Met Glu Tyr Ala Asn Gly Gly Glu Leu Phe Phe His Leu Ser
                                                220
                         230
                                           235
     Arg Glu Arg Val Phe Ser Glu Asp Arg Ala Arg Phe Tyr Gly Ala Glu
50
                                        250
     Ile Val Ser Ala Leu Asp Tyr Leu His Ser Glu Lys Asn Val Val Tyr
                                    265
     Arg Asp Leu Lys Leu Glu Asn Leu Met Leu Asp Lys Asp Gly His Ile
55
                    280
     Lys Ile Thr Asp Phe Gly Leu Cys Lys Glu Gly Ile Lys Asp Gly Ala
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		290					295					300				
	Thr		Lys	Thr	Phe	Сув		Thr	Pro	Glu	Tvr		Ala	Pro	Glu	Val
	305		-			310	•				315					320
5	Leu	Glu	Asp	Asn	Asp 325	Tyr	Gly	Arg	Ala	Val 330	Asp	Trp	Trp	Gly	Leu 335	Gly
	Val	Val	Met	Tyr 340	Glu	Met	Met	Сув	Gly 345		Leu	Pro	Phe	Tyr 350		Gln
	Asp	His	Glu 355		Leu	Phe	Glu	Leu 360		Leu	Met	Glu	Glu 365		Arg	Phe
10	Pro	Arg 370		Leu	Gly	Pro	Glu 375		Lys	Ser	Leu	Leu 380		Gly	Leu	Leu
	Lys 385		Asp	Pro	Lys	Gln 390		Leu	Gly	Gly	Gly 395		Glu	qaA	Ala	Lys 400
		Ile	Met	Gln	His		Phe	Phe	Ala	Glv		Va 1	Tro	Gln	His	
15					405					410		,,,			415	
	Tyr	Glu	Lys	Lys 420	Leu	Ser	Pro	Pro	Phe 425	Lys	Pro	Gln	Val	Thr 430	Ser	Glu
	Thr	Asp	Thr 435	Arg	Tyr	Phe	Asp	Glu 440	Glu	Phe	Thr	Ala	Gln 445	Met	Ile	Thr
20		450			Asp		455	_				460		-		
	465				Phe	470					475					480
25					Val 485					490					495	
				500	Pro				505					510		
			515		Val			520					525			
30		530			Lys		535					540				
	545				Val	550					555					560
35					His 565					570					575	
				580	Val				585					590		
40			595		Arg			600					605			
40		610			Leu -		615					620				
	625				Leu	630					635					640
45					Gln 645					650					655	
				660	Asp				665					670		
50			675		Gly			680					685			
30		690			Ser		695					700				
	705				Leu	710	Pne	val	Thr	Ala	Ala 715	GIA	IIe	Thr	Leu	Gly 720
55	mec	Asp	GIU	ьeu	Tyr 725	ьуs										

160

	(2) INFORMATION FOR SEQ ID NO:72:	
5	(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 2751 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear	
10	(ii) MOLECULE TYPE: cDNA (ix) FEATURE:	
15	(A) NAME/KEY: Coding Sequence(B) LOCATION: 12748(D) OTHER INFORMATION:(xi) SEQUENCE DESCRIPTION: SEQ ID NO:72:	
20	ATG GCT GAC GTT TAC CCG GCC AAC GAC TCC ACG GCG TCT CAG GAC GTG Met Ala Asp Val Tyr Pro Ala Asn Asp Ser Thr Ala Ser Gln Asp Val 1 5 10 15	48
25	GCC AAC CGC TTC GCC CGC AAA GGG GCG CTG AGG CAG AAG AAC GTG CAT Ala Asn Arg Phe Ala Arg Lys Gly Ala Leu Arg Gln Lys Asn Val His 20 25 30	96
	GAG GTG AAA GAC CAC AAA TTC ATC GCC CGC TTC TTC AAG CAA CCC ACC Glu Val Lys Asp His Lys Phe Ile Ala Arg Phe Phe Lys Gln Pro Thr 40	144
30	TTC TGC AGC CAC TGC ACC GAC TTC ATC TGG GGG TTT GGG AAA CAA GGC Phe Cys Ser His Cys Thr Asp Phe Ile Trp Gly Phe Gly Lys Gln Gly 50 55 60	192
35	TTC CAG TGC CAA GTT TGC TGT TTT GTG GTT CAT AAG AGG TGC CAT GAG Phe Gln Cys Gln Val Cys Cys Phe Val Val His Lys Arg Cys His Glu 70 75 80	240
40	TTC GTT ACG TTC TCT TGT CCG GGT GCG GAT AAG GGA CCT GAC ACT GAC Phe Val Thr Phe Ser Cys Pro Gly Ala Asp Lys Gly Pro Asp Thr Asp 85 90 95	288
45	GAC CCC AGG AGC AAG CAC AAG TTC AAA ATC CAC ACA TAC GGA AGC CCT Asp Pro Arg Ser Lys His Lys Phe Lys Ile His Thr Tyr Gly Ser Pro 100 105 110	336
	ACC TTC TGT GAT CAC TGT GGG TCC CTG CTC TAT GGA CTT ATC CAC CAA Thr Phe Cys Asp His Cys Gly Ser Leu Leu Tyr Gly Leu Ile His Gln 115 120 125	384
50	GGG ATG AAA TGT GAC ACC TGC GAC ATG AAT GTT CAC AAC CAG TGT GTG Gly Met Lys Cys Asp Thr Cys Asp Met Asn Val His Asn Gln Cys Val	432

160

480

160

Gly Met Lys Cys Asp Thr Cys Asp Met Asn Val His Asn Gln Cys Val

ATC AAT GAC CCT AGC CTC TGC GGA ATG GAT CAC ACA GAG AAG AGG GGG

Ile Asn Asp Pro Ser Leu Cys Gly Met Asp His Thr Glu Lys Arg Gly

155

135

150

161

	୯୯୯	Δ ጥ	тат	СТС	AAG	GCT	GNG	GTC	ልርጥ	GAT	GAA	AAG	כידיני	CAC	GTC	ACG	528
					Lys 165												320
5																	
					AAA												576
	vai	Arg	Asp	180	Lys	Asn	Leu	TIE	185	мес	Asp	Pro	Asn	190	Leu	ser	
10	GAT	CCT	TAT	GTG	AAG	CTG	AAA	CTA	ATC	CCT	GAC	CCC	AAG	AAT	GAG	AGC	624
	Asp	Pro	Tyr 195	Val	Lys	Leu	Lys	Leu 200	Ile	Pro	Asp	Pro	Lys 205	Asn	Glu	Ser	
	AAA	CAG	AAA	ACC	AAA	ACC	ATC	CGC	TCC	AAC	CTG	AAT	CCT	CAG	TGG	AAT	672
15	Lys	Gln 210	Lys	Thr	Lys	Thr	Ile 215	Arg	Ser	Asn	Leu	Asn 220	Pro	Gln	Trp	Asn	
	GAG	TCC	TTC	ACG	TTC	AAA	TTA	AAA	CCT	TCA	GAC	AAA	GAC	CGG	CGA	CTG	720
		Ser	Phe	Thr	Phe	-	Leu	Lys	Pro	Ser	-	Lys	Asp	Arg	Arg		
20	225					230					235					240	
					TGG												768
	ser	vaı	GIU	тте	Trp 245	Asp	Trp	Asp	Arg	7nr 250	Thr	Arg	Asn	Asp	255	Met	
25					2.0												
	GGA	TCC	CTT	TCC	TTT	GGT	GTC	TCA	GAG	CTA	ATG	AAG	ATG	CCG	GCC	AGT	816
	Gly	Ser	Leu		Phe	Gly	Val	Ser		Leu	Met	ГÀв	Met		Ala	Ser	
				260					265					270			
30	GGA	TGG	TAT	AAA	GCT	CAC	AAC	CAA	GAA	GAG	GGC	GAA	TAT	TAC	AAC	GTG	864
	Gly	Trp	_	Lys	Ala	His	Asn		Glu	Glu	Gly	Glu	-	Tyr	Asn	Val	
			275					280					285				
	CCC	ATT	CCA	GAA	GGA	GAT	GAA	GAA	GGC	AAC	ATG	GAA	CTC	AGG	CAG	AAG	912
35	Pro		Pro	Glu	Gly	Asp		Glu	Gly	Asn	Met		Leu	Arg	Gln	Lys	
		290					295					300					
					AAG												960
40	Phe 305	Glu	Lys	Ala	Lys	Leu 310	Gly	Pro	Val	Gly		Lys	Val	Ile	Ser	Pro 320	
40	303					310					315					320	
	TCA	GAA	GAC	AGA	AAG	CAA	CCA	TCC	AAC	AAC	CTG	GAC	AGA	GTG	AAA	CTC	1008
	Ser	Glu	Asp	Arg	ГÀЗ	Gln	Pro	Ser	Asn		Leu	Asp	Arg	Val	_	Leu	
45					325					330					335		
40	ACA	GAC	TTC	AAC	TTC	CTC	ATG	GTG	CTG	GGG	AAG	GGG	AGT	TTT	GGG	AAG	1056
					Phe												
				340					345					350			
50	GTG	ATG	Слл	GCT	GAC	AGG	מאמ	GGA	ACG	GAG	GAD	ርጥር	דאר	GCC	ልጥሮ	AAG	1104
00					Asp												1104
			355		-	-	-	360					365			-	
	ATC	СТС	AAG	AAG	GAC	GTG	GTG	ATC	CAG	GAC	GAC	GAC	GTG	GAG	TGC	ACC	1152
55	•				Asp												
		370					375					380					

5	38	35					3	90	пец	MI	a Lit	eu 1	Leu	39 <u>5</u>	Ly 5	s P	ro	Pro) Pi	ne	CTG Leu 400	1200
	AC Th	r G	AG Iln	Let	G CA 1 Hi	C T(S Se 4(gc ys	TTC Phe	CA Gl:	G AC	ır v	TG al	GAC Asp	C CG	g C	TG eu	ТАС	TT Ph	ıe	GTC Val	1248
10	AT Me	'G G t G	AA lu	TAC Tyr	GT (Va. 42)	C AA l As	.C G n G	GC (GGG 31y	GA:	CT Le 42	u M	TG let	TAC Tyr	CA:	C A	TT le	CAG Gln 430	G1	A n	GTC Val	1296
15			-	435			- .		,111	440	va	т Р.	ne	Tyr	Ala	4 A	la IS	Glu	Il.	е .	Ser	1344
20		4 5	50		TT(4	55	пув	Ar	g G.	ıy	He	11e	ту	r	Arg	Ası	p]	Leu	1392
25	465	5			AAT Asn	, , ,	47	0	eu.	ASN	sei	: G1	Lu (31y 475	His	Il	e I	ъys	Ιlε	≥ <i>I</i> 4	Ala 180	1440
	GAC Asp	TT Ph	ie G	egg Ely	ATG Met	TGC Cys 485	-7	G G	AA (lu I	CAC His	ATO	AT Me 49	et A	GAT Asp	GGA Gly	GT Va	C #	ACG hr	ACC Thr 495	A	igg irg	1488
30	ACC Thr	TT Ph	C T e C		GGA Gly 500	ACT Thr	Pr	G GA	AC 7	rac ryr	ATT Ile 505	AI	C C	CCA Pro	GAG Glu	ATZ Ile	e I	TC le 10	GCT Ala	T	'AC 'yr	1536
35	CAG Gln	Pro	G T.	AC yr 15	GGG Gly	AAG Lys	TC'	r Gi	1 A	AT sp 20	TGG Trp	TG:	G G p A	CG '	TAC Tyr	GG7 G1y 525	, A	TG al	CTG Leu	L.	TG eu	1584
40	TAC Tyr	GAG Glu 530	G A' 1 Me	TG (et]	CTA Leu	GCC Ala	GGC Gly	G CA Gl 53	11 P	CT ro	CCG Pro	TT:	r G	gp (GGT Gly	GAA Glu	G. A	AT (GAA Glu	G/As	AT sp	1632
45	GAA Glu 545						550	116	c G.	ıu .	HIS	Asn	1 Vá	al S 55	er	Tyr	Pı	o I	ys	Se	er 50	1680
50	TTG Leu		_		!	565		50.		ie (-ys	ьуs 570	G	Ly L	eu i	Met	Th	ır I 5	ys 75	Gl	n.	1728
50	Pro .			5	80		o i j	Cyr	, 61	.y <u>.</u>	85	Glu	GI	y G	lu A	Arg	As 59	р V 0	al	Ar	g	1776
55	GAG (CAT His	GC A1. 59	C T a P 5	TC 1	TTC . Phe .	AGG Arg	AGG Arg	AT 11 60	e A	AC .sp	TGG Trp	GA G1	G A	ys I	CTG Leu 105	GA Gl	GA uA	AC .	AG Ar	g g	1824

		Ile		CCA Pro			Lys					Gly					1872
_		610					615					620					
5	770	thathat.	CAC	AAG	THE C	TTTC	N.C.C.	CCA	CCA	CNC	CCT	CTC	מיחית	א כי א	CCN	CCA	1920
				Lys													1920
	625	FIIC	пор	шуз	1110	630	1111	ni 9	dry	0111	635	VUI				640	
	023										***						
10	GAT	CAG	CTG	GTC	ATT	GCT	AAC	ATA	GAC	CAA	TCT	GAT	TTT	GAA	GGG	TTC	1968
	Asp	Gln	Leu	Val	I·le	Ala	Asn	Ile	Asp	Gln	Ser	Asp	Phe	Glu	Gly	Phe	
					645					650					655		
4-				AAC													2016
15	Ser	Tyr	Val	Asn	Pro	GIn	Phe	Val		Pro	Ile	Leu	GIn		Ala	vaı	
				660					665					670			
	GGG	ccc	GCC	ATG	ΔСТ	ααα	GGA	GAA	GAD	СТТ	יייייי	Δርጥ	GGA	GTT	GTC	CCA	2064
				Met													2001
20	1	5	675			-1-	1	680					685				
	ATT	CTT	GTT	GAA	$\mathbf{T}\mathbf{T}\mathbf{A}$	GAT	GGC	GAT	GTT	AAT	GGG	CAA	AAA	TTC	TCT	GTT	2112
	Ile	Leu	Val	Glu	Leu	Asp	Gly	Asp	Val	Asn	Gly	Gln	Lys	Phe	Ser	Val	
		690					695					700					
25																	
				GGT													2160
		GIY	GIU	Gly	GIU	-	Asp	АТа	Thr	Tyr	-	гÀв	Leu	Tnr	Leu	ьуs 720	
	705					710					715					720	
30	ттт	ATT	TGC	ACT	ACT	GGG	AAG	СТА	CCT	GTT	CCA	TGG	CCA	ACG	CTT	GTC	2208
•				Thr												_	
			•		725	•	•			730		-			735		
	ACT	ACT	CTC	ACT	TAT	GGT	GTT	CAA	TGC	TTT	TCT	AGA	TAC	CCA	GAT	CAT	2256
35	Thr	Thr	Leu	Thr	Tyr	Gly	Val	Gln	-	Phe	Ser	Arg	Tyr		Asp	His	
				740					745					750			
	א תרכו	7 7 7 T	C A C	C N III	ana	നനന	TTTC	220	N COTT	000	א יייטריו	aaa	C 7 7	COM	ייי מייי	CTA	2304
				CAT His												_	2304
40	Mec	цуъ	755	nis	мар	FIIC	FIIC	760	Ser	AIG	Mec	FIU	765	Gry	1 7 1	vai	
.0													, 05				
	CAG	GAA	AGA	ACT	ATA	TTT	TAC	AAA	GAT	GAC	GGG	AAC	TAC	AAG	ACA	CGT	2352
	Gln	Glu	Arg	Thr	Ile	Phe	Tyr	Lys	Asp	Asp	Gly	Asn	Tyr	Lys	Thr	Arg	
		770					775					780					
45																	
				AAG													2400
		GIu	vaı	Lys	Phe		GIY	Asp	Thr	Leu		Asn	Arg	IIe	GIU		
	785					790					795					800	
50	ααα	GGT	ערידע	GAT	սեւսեւ	מממ	GAA	САТ	GGA	אאר	מייים	CTT	GGA	CAC	ααα	ATG	2448
00				Asp													
	- _I J	1			805				1	810					815	•	
	GAA	TAC	AAT	TAT	AAC	TCA	CAT	AAT	GTA	TAC	ATC	ATG	GCA	GAC	AAA	CCA	2496
55	Glu	Tyr	Asn	Tyr	Asn	Ser	His	Asn	Val	Tyr	Ile	Met	Ala	Asp	Lys	Pro	
				820					825					830			

5				835		2				TTC Phe 840	: цу:	5 I	ie /	Arg	His	As 84	n I 5	le	Lys	Asp		4
	G	ga :	AGC Ser 850	GTT Val	CA.	A TT	A G		GAC Asp 855	CAT His	ТА: Туз	r C	AA (ln (31n	AAT Asn 860	AC Th	r C	CA ro	ATT Ile	GGC Gly	259	2
10	86	55	•				87	70	10	GAC Asp	ASI	L H	.s 1	'yr 175	Leu	Sei	T	hr	Gln	Ser 880		0
15	G(A]	CC C	TT eu	TCC Ser	AAA Lys	GA' As ₁ 885		C A	AC	GAA Glu	AAG Lys	Ar Ar	g A	AT (CAC His	ATO Met	AT	le :	CTT Leu 895	CTT Leu	2688	3
20	GA G1	G T u P	TT he	GTA Val	ACA Thr 900	GC1 Ala	GC Al	T G a G	GG ly	ATT Ile	ACA Thr 905	CA Hi	T G	GC A	ATG Met	GAT Asp	G# G1 91	.u 1	CTA Leu	TAC Tyr	2736	i
25	AA Ly	A C	ro (CAG Gln 915	GAG Glu	TAA															275	1
										SEQ		NO:	73 :									
30			(SE(A) 1 B) 1 C) 5 D) 1	LENG TYPE STRA	TH: : an NDEI	916 minc ONES	am ac S:	ninc id sin	STIC ac:	CS: ids											
35			(ii) MC	LEC	ULE	TYP	E:	pro	teir rnal	1											
40										ON:												
40										sn A												
										ly A 2 le A												
45	Phe	Cys	35 Se	r H	is C	ys	Thr	Asp	4 (Ph	ne I	le 1	rp	Gly	Ph	e 1.5 4.5 e G.3	ys (5 Ly 1	vs J	Pr Gl	o Tl	hr		
	Phe 65	Glr	1 Су	s G	ln V	al (Cys 70	Cys	Ph	e V	al V	al	His	60 Ly.	s Aı	g (:ys	Hi	s G]	Lu		
50	Phe	Val	. Th	r Pł	ne S 8	er (Cys	Pro	G1	у А	la A 9	sp 0	75 Lys	Gl	y Pr	O P	sp	Th	80 r As) Sp		
	Asp Thr	Phe	Ar Cv	g Se 10 s As	r L	ys I	lis	Lys	Ph	e Ly	/s I)5	le	His	Th	г Ту	r G	ly 10	Se:	r Pr	0		
55	Thr Gly	Met	11. Ly:	5 5 Cy	s As	sp T	hr	сла	Se 12 As	r Le O D Me	eu L	eu sn	Tyr Vəl	Gl _y	/ Le	u I 5	le	Hi:	s Gl	n		
								-			- 11		· a 1	1175	, AS	11 G	тn	СУ	s Va	1		

		130	_	_			135	0.7				140	~ 3			~ 1
		Asn	Asp	Pro	ser	ьеи 150	Cys	GTA	Met	Asp	155	Thr	GIU	гув	Arg	160
	145	Tla	Tyr	Lou	Lare		Glu	Val	Thr	Nen		Larg	T.011	Hic	Wal.	
5	AIG	116	TYL	Deu	165	AIG	GIU	Val	1111	170	Giu	цув	Бец	пть	175	1111
·	Val	Ara	Asp	Ala		Asn	Leu	Ile	Pro		Asp	Pro	Asn	Glv		Ser
		3		180					185					190		
	Asp	Pro	Tyr	Val	Lys	Leu	Lys	Leu	Ile	Pro	Asp	Pro	Lys	Asn	Glu	Ser
			195					200					205			
10	Lys	Gln	Lys	Thr	Lys	Thr	Ile	Arg	Ser	Asn	Leu	Asn	Pro	Gln	Trp	Asn
		210					215					220				
		Ser	Phe	Thr	Phe	-	Leu	Lys	Pro	Ser	-	Lys	Asp	Arg	Arg	
	225		~-3		_	230	_	_	_		235	_	_	_	~)	240
15	ser	vaı	Glu	11e	245	Asp	Trp	Asp	Arg	250	unr	arg	Asn	Asp	255	met
15	Glv	Ser	Leu	Ser		Glv	Val	Ser	Glu		Met	Lave	Met	Pro		Ser
	Gry	Ser	пси	260	FIIC	Gry	Val	JCI	265	шец	Mec	БУБ	rice	270	AIG	561
	Glv	Trp	Tyr		Ala	His	Asn	Gln	_	Glu	Gly	Glu	Tyr		Asn	Val
	_	•	275	•	,			280			•		285	-		
20	Pro	Ile	Pro	Glu	Gly	Asp	Glu	Glu	Gly	Asn	Met	Glu	Leu	Arg	Gln	Lys
		290					295					300				
		Glu	Lys	Ala	Lys		Gly	Pro	Val	Gly		Lys	Val	Ile	Ser	
	305	_				310					315					320
O.F.	Ser	Glu	Asp	Arg	-	Gln	Pro	Ser	Asn		Leu	Asp	Arg	Val	-	Leu
25	Thr	7 an	Phe	Nan	325	Lou	Mot	V-1	Ι	330	Tara	C111	cor	Dhe	335	Luc
	1111	Asp	PHE	340	PHE	Leu	Mec	vai	345	СТУ	ъу	СТУ	261	350	СТУ	цуъ
	Val	Met	Leu		qaA	Arq	Lys	Gly		Glu	Glu	Leu	Tyr		Ile	Lys
			355		•		•	360					365			-
30	Ile	Leu	Lys	Lys	Asp	Val	Val	Ile	Gln	Asp	Asp	Asp	Val	${\tt Glu}$	Cys	Thr
		370					375					380				
		Val	Glu	Lys	Arg		Leu	Ala	Leu	Leu	_	Lys	Pro	Pro	Phe	
	385	01 -			0	390	nh-	a1-	m)	**- 1	395	3	7		Db -	400
35	ınr	GIN	Leu	HIS	405	Cys	Pne	GIN	Inr	vai 410	Asp	Arg	Leu	Tyr	415	vaı
33	Met	Glu	Tyr	Val		Glv	Glv	Δsn	Len		ጥህጕ	Hie	Tle	Gln		Val
		014	- / -	420	*****	O.	Cly	p	425	1100	- 7 -	*****	110	430	0	V 44 2
	Gly	Lys	Phe		Glu	Pro	Gln	Ala		Phe	Tyr	Ala	Ala		Ile	Ser
	-	-	435	-				440			-		445			
40	Ile	Gly	Leu	Phe	Phe	Leu	His	Lys	Arg	Gly	Ile	Ile	Tyr	Arg	Asp	Leu
		450			_		455			_		460	_		_	
	_	Leu	Asn	Asn	Val		Leu	Asn	Ser	Glu	_	His	Ile	Lys	Ile	
	465	Dha	<i>α</i> 1	Mot	C	470	C 1	mi a	Mak	Mob	475	G1	37-3	mb-~	Thr	480
45	Asp	Pne	Gly	Mec	485	ьys	GIU	HIS	Mec	490	Asp	GIA	vai	Inr	495	Arg
40	Thr	Phe	Cys	Glv		Pro	Asp	Tvr	Ile		Pro	Glu	Tle	Tle		Tvr
			-,-	500			F	- , -	505					510		-2-
	Gln	Pro	Tyr	Gly	Lys	Ser	Val	Asp	Trp	Trp	Ala	Tyr	Gly	Val	Leu	Leu
			515					520				_	525			
50	Tyr		Met	Leu	Ala	Gly		Pro	Pro	Phe	Asp		Glu	Asp	Glu	Asp
		530			_		535			_		540	_		_	
		Leu	Phe	Gln	Ser		Met	Glu	His	Asn		Ser	Tyr	Pro	ГÀЗ	
	545 Lev	cc~	Lys	<i>G</i> 1	λ Ι~	550 Val	Se~	τ1	Cvc	Lare	555	Lev	Mot	Th~	Lare	560 Gln
55	neu	ser	гув	GIU	565	vall	Ser	тте	Cys	ьув 570	GTÅ	րգն	met	Inc	БУВ 575	3111
	Pro	Ala	Lys	Ara		Glv	Cvs	Glv	Pro		Glv	Glu	Ara	Asp		Arq
	_				_	-	4	- 4		_	-			- 1	-	_

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580
                                     585
      Glu His Ala Phe Phe Arg Arg Ile Asp Trp Glu Lys Leu Glu Asn Arg
                          600
                                                   605
      Glu Ile Gln Pro Pro Phe Lys Pro Lys Val Cys Gly Lys Gly Ala Glu
  5
                              615
                                               620
      Asn Phe Asp Lys Phe Phe Thr Arg Gly Gln Pro Val Leu Thr Pro Pro
                         630
                                             635
      Asp Gln Leu Val Ile Ala Asn Ile Asp Gln Ser Asp Phe Glu Gly Phe
                     645
                                        650
      Ser Tyr Val Asn Pro Gln Phe Val His Pro Ile Leu Gln Ser Ala Val
 10
                                     665
      Gly Arg Ala Met Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro
                                680
      Ile Leu Val Glu Leu Asp Gly Asp Val Asn Gly Gln Lys Phe Ser Val
15
                            695
                                                 700
      Ser Gly Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys
                        710
                                  715
      Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val
                                        730
      Thr Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His
20
                 740
                                    745
      Met Lys Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val
                         760
      Gln Glu Arg Thr Ile Phe Tyr Lys Asp Asp Gly Asn Tyr Lys Thr Arg
25
                             775
                                                780
      Ala Glu Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu
                         790
                                            795
     Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Met
                    805
                                        810
     Glu Tyr Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Pro
30
                                   825
     Lys Asn Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Lys Asp
                               840
     Gly Ser Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly
35
                            855
                                               860
     Asp Gly Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser
               870
                                           875
     Ala Leu Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Ile Leu Leu
                    885
                                       890
     Glu Phe Val Thr Ala Ala Gly Ile Thr His Gly Met Asp Glu Leu Tyr
40
                900
     Lys Pro Gln Glu
            915
45
              (2) INFORMATION FOR SEQ ID NO:74:
           (i) SEQUENCE CHARACTERISTICS:
             (A) LENGTH: 2157 base pairs
             (B) TYPE: nucleic acid
50
             (C) STRANDEDNESS: single
             (D) TOPOLOGY: linear
           (ii) MOLECULE TYPE: cDNA
           (ix) FEATURE:
```

(A) NAME/KEY: Coding Sequence

167

(B) LOCATION: 1...2154(D) OTHER INFORMATION:

(xi) SEOUENCE DESCRIPTION: SEO ID NO:74:

5		()	ki) S	SEQUI	ENCE	DESC	CRIP	CION	: SE() ID	NO:	74:					
	ATG	TCG	TCC	ATC	TTG	CCA	TTC	ACG	CCG	CCA	GTT	GTG	AAG	AGA	CTG	CTG	48
	Met	Ser	Ser	Ile	Leu	${\tt Pro}$	Phe	Thr	Pro	Pro	Val	Val	Lys	Arg	Leu	Leu	
	1				5					10					15		
10					ma.	aam	com	~~~			~~~					a.a	0.5
10					TCA												96
	GIY	тър	цуз	ப்ரத 20	Ser	мта	GIY	GIA	25	GIY	Gly	AIA	СТУ	30	Gry	Giu	
	CAG	AAT	GGG	CAG	GAA	GAA	AAG	TGG	TGT	GAG	AAA	GCA	GTG	AAA	AGT	CTG	144
15	Gln	Asn	Gly	Gln	Glu	Glu	Lys	Trp	Cys	Glu	Lys	Ala	Val	Lys	Ser	Leu	
			35					40					45				
	CTC	አአር	אאמ	СТА	AAG	מממ	אכא	GGV	CGN	ጥጥለ	ር አጥ	GNG	Curr	GNG	מממ	GCC	192
					Lys												172
20		50	-1-		-1	_,_	55	1				60			-1-		
					AAC												240
	11e 65	Thr	Thr	Gln	Asn	Cys 70	Asn	Thr	Lys	Cys		Thr	Ile	Pro	Ser	Thr 80	
25	65					70					75					80	
	TGC	TCT	GAA	ATT	TGG	GGA	CTG	AGT	ACA	CCA	AAT	ACG	ATA	GAT	CAG	TGG	288
					Trp												
					85					90					95		
20	~~~				amm	m										a.m	226
30					CTT Leu												336
	лор	1111	1111	100	Deu	- y -		1110	105	Giu	OIII	1111	Arg	110	пси	vab	
	GGT	CGT	CTC	CAG	GTA	TCC	CAT	CGA	AAA	GGA	TTG	CCA	CAT	GTT	ATA	TAT	384
35	Gly	Arg		Gln	Val	Ser	His	_	Lys	Gly	Leu	Pro		Val	Ile	Tyr	
			115					120					125				
	TGC	CGA	TTA	TGG	CGC	TGG	ССТ	GAT	СТТ	CAC	AGT	CAT	CAT	GAA	CTC	AAG	432
					Arg												
40		130					135	_				140					
	_				TGC												480
	145	TTE	GIU	ASII	Cys	150	Tyr	Ата	Pne	Asn	155	гур	гаг	Asp	GIU	160	
45	113	•				130					133					100	
	TGT	GTA	AAC	CCT	TAC	CAC	TAT	CAG	AGA	GTT	GAG	ACA	CCA	GTT	TTG	CCT	528
	Cys	Val	Asn	Pro	Tyr	His	Tyr	Gln	Arg	Val	Glu	Thr	Pro	Val	Leu	Pro	
					165					170					175		
50	CCA	GTD	ጥጥል	GTG	CCC	CGA	CAC	ACC	GNG	ልጥሮ	מיזיים	ACA	CDD	سبن	CCG	ССТ	576
00					Pro												370
				180		-			185					190			
E E					ACT												624
55	ьeu	Asp	195	ıyr	Thr	HIS	ser	11e 200	Pro	GIU	Asn	Thr	Asn 205	Pne	Pro	Ala	
			100					200					200				

5		672
	TAT ATC AGT GAA GAT GGA GAA ACA AGT GAC CAA CAG TTG AAT CAA AGT Tyr Ile Ser Glu Asp Gly Glu Thr Ser Asp Gln Gln Leu Asn Gln Ser 230 235 240	720
10	ATG GAC ACA GGC TCT CCA GCA GAA CTA TCT CCT ACT ACT CTT TCC CCT Met Asp Thr Gly Ser Pro Ala Glu Leu Ser Pro Thr Thr Leu Ser Pro 245 250 255	768
15	GTT AAT CAT AGC TTG GAT TTA CAG CCA GTT ACT TAC TCA GAA CCT GCA Val Asn His Ser Leu Asp Leu Gln Pro Val Thr Tyr Ser Glu Pro Ala 260 265 270	816
20	TTT TGG TGT TCA ATA GCA TAT TAT GAA TTA AAT CAG AGG GTT GGA GAA Phe Trp Cys Ser Ile Ala Tyr Tyr Glu Leu Asn Gln Arg Val Gly Glu 275 280 285	864
25	ACC TTC CAT GCA TCA CAG CCC TCA CTC ACT GTA GAT GGC TTT ACA GAC Thr Phe His Ala Ser Gln Pro Ser Leu Thr Val Asp Gly Phe Thr Asp 290 295 300	912
	CCA TCA AAT TCA GAG AGG TTC TGC TTA GGT TTA CTC TCC AAT GTT AAC Pro Ser Asn Ser Glu Arg Phe Cys Leu Gly Leu Leu Ser Asn Val Asn 305 310 315 320	960
30	CGA AAT GCC ACG GTA GAA ATG ACA AGA AGG CAT ATA GGA AGA GGA GTG Arg Asn Ala Thr Val Glu Met Thr Arg Arg His Ile Gly Arg Gly Val 325 330 335	1008
35	CGC TTA TAC TAC ATA GGT GGG GAA GTT TTT GCT GAG TGC CTA AGT GAT Arg Leu Tyr Tyr Ile Gly Gly Glu Val Phe Ala Glu Cys Leu Ser Asp 340 350	1056
40	AGT GCA ATC TTT GTG CAG AGC CCC AAT TGT AAT CAG AGA TAT GGC TGG Ser Ala Ile Phe Val Gln Ser Pro Asn Cys Asn Gln Arg Tyr Gly Trp 355 360 365	1104
45	370 375 Pro Pro Gly Cys Asn Leu Lys Ile 380	1152
	385 390 Leu Leu Ala Gln Ser Val Asn Gln 395 400	1200
50	GGT TTT GAA GCC GTC TAT CAG CTA ACT AGA ATG TGC ACC ATA AGA ATG Gly Phe Glu Ala Val Tyr Gln Leu Thr Arg Met Cys Thr Ile Arg Met 405 410 415	.248
55	AGT TTT GTG AAA GGG TGG GGA GCA GAA TAC CGA AGG CAG ACG GTA ACA Ser Phe Val Lys Gly Trp Gly Ala Glu Tyr Arg Arg Gln Thr Val Thr 420 425 430	296
		100

5				ATT Ile						1344
3				ACT Thr						1392
10				CCG Pro 470						1440
15				GAG Glu						1488
20				GTA Val						1536
25				ACC Thr						1584
				CCC Pro						1632
30				TGC Cys 550						1680
35				TCC Ser						1728
40	_	_	_	GAC Asp						1776
45				ACC Thr						1824
				GGC Gly						1872
50				GTC Val 630						1920
55	_			AAG Lys	_					1968

5					660		-72	0111	GI	66	55 T	nr P	ro 1	le o	Sly F	sp (lly		2016
	v	al L	eu	Leu 675	Pro	Asp	AAC Asn	CAC His	TA:	r Le	CG AC	GC A	CC C hr G	ln S	CC G er A 85	CC C	TG eu	AGC Ser	2064
10		6	90				AAG Lys	695	ASĻ) HI	S Me	et Va	al L 7	eu L 00	eu G	lu P	he	GTG Val	2112
15	A(T) 7(CC (GCC Ala	GGG .	-10	ACT Thr 710	CTC Leu	GGC Gly	AT Me	G GA t As	.C G/ p G] 71	lu L	TG T	AC A yr L	AG T. ys	AA		2157
20			(i)	SE	QUEN	CE C	TION HARA	CTER	IST	ICS		:75:							
25			(B) 7 C) 5 D) 7	TYPE: TRAN TOPOI	: am: IDEDI LOGY	718 ; ino ; NESS : lii	acid : si near	ngl	е	3								
			(ii (v)) MC FRA	LECU GMEN	ILE T	TYPE:	inte	erna	in al									
30			(xi) SE	QUEN	CE D	ESCF	RIPT	ON:	SE	Q II	NO.	:75:						
35							ro F												
							lu L			Cys									
40							ys T 5												
							ys A O												
							ly L												
45	Gly	7~~		10	.у це	:u 1)	yr Se	er P.	he :	Ser 105	Glu	Gln	Thr	Arg	Ser 110	Lev	ı A:	sp	
							er H:												
50							rp Pi 13												
							u Ty												
							. в Ту					Glu							
55							g Hi			lu	Ile								
	Leu	Asp	Asp	Ty	r Th	r Hi	s Se	r 11	e P	ro	Glu	Asn	Thr	Asn	Dho	D			

			195					200					205			
	Gly	Ile 210	Glu	Pro	Gln	Ser	Asn 215	Tyr	Ile	Pro	Glu	Thr 220	Pro	Pro	Pro	Gly
5	Tyr 225	Ile	Ser	Glu	Asp	Gly 230		Thr	Ser	Asp	Gln 235		Leu	Asn	Gln	Ser 240
-		Asp	Thr	Gly	Ser 245		Ala	Glu	Leu	Ser 250		Thr	Thr	Leu	Ser 255	
•	Val	Asn	His	Ser 260	_	Asp	Leu	Gln	Pro 265		Thr	Tyr	Ser	Glu		Ala
10	Phe	Trp	-		Ile	Ala	Tyr	-		Leu	Asn	Gln	_	270 Val	Gly	Glu
	Thr		275 His	Ala	Ser	Gln		280 Ser	Leu	Thr	Val	-	285 Gly	Phe	Thr	Asp
	D	290	71	0	a1	7	295	C	Υ	a 3	T	300	0		**- 1	3
15	305					310		-		-	315			Asn		320
					325					330				Arg	335	
				340					345					Leu 350		
20	Ser	Ala	11e 355	Phe	Val	Gln	Ser	Pro 360	Asn	Cys	Asn	Gln	Arg 365	Tyr	Gly	Trp
	His	Pro 370	Ala	Thr	Val	Cys	Lys 375	Ile	Pro	Pro	Gly	380	Asn	Leu	Lys	Ile
25	385					390					395			Val		400
	Gly	Phe	Glu	Ala	Val 405	Tyr	Gln	Leu	Thr	Arg 410	Met	Cys	Thr	Ile	Arg 415	Met
	Ser	Phe	Val	Lys 420	Gly	Trp	Gly	Ala	Glu 425	Tyr	Arg	Arg	Gln	Thr 430	Val	Thr
30	Ser	Thr	Pro 435	Cys	Trp	Ile	Glu	Leu 440	His	Leu	Asn	Gly	Pro 445	Leu	Gln	Trp
	Leu	Asp 450	Lys	Val	Leu	Thr	Gln 455	Met	Gly	Ser	Pro	Ser 460	Val	Arg	Cys	Ser
35	Ser 465	Met	Ser	Trp	Val	Pro 470	Arg	Ala	Arg	Asp	Pro 475	Pro	Val	Ala	Thr	Met 480
	Val	Ser	Lys	Gly	Glu 485	Glu	Leu	Phe	Thr	Gly 490	Val	Val	Pro	Ile	Leu 495	Val
	Glu	Leu	Asp	Gly 500	Asp	Val	Asn	Gly	His 505	Lys	Phe	Ser	Val	Ser 510	Gly	Glu
40	Gly	Glu	Gly 515	Asp	Ala	Thr	Tyr	Gly 520	Lys	Leu	Thr	Leu	Lys 525	Phe	Ile	Cys
	Thr	Thr 530	Gly	Lys	Leu	Pro	Val 535	Pro	Trp	Pro	Thr	Leu 540	Val	Thr	Thr	Leu
45	Thr 545	Tyr	Gly	Val	Gln	Cys 550	Phe	Ser	Arg	Tyr	Pro 555	Asp	His	Met	Lys	Gln 560
	His	Asp	Phe	Phe	Lys 565	Ser	Ala	Met	Pro	Glu 570	Gly	Tyr	Val	Gln	Glu 575	Arg
	Thr	Ile	Phe	Phe 580	Lys	Asp	Asp	Gly	Asn 585	Tyr	Lys	Thr	Arg	Ala 590	Glu	Val
50	Lys	Phe	Glu 595	Gly	Asp	Thr	Leu	Val 600	Asn	Arg	Ile	Glu	Leu 605	Lys	Gly	Ile
	Asp	Phe 610	Lys	Glu	Asp	Gly	Asn 615		Leu	Gly	His	Lys 620		Glu	Tyr	Asn
55	Tyr 625	Asn	Ser	His	Asn	Val 630	Tyr	Ile	Met	Ala	Asp 635	Lys	Gln	Lys	Asn	Gly 640
	Ile	Lys	Val	Asn	Phe	Lys	Ile	Arg	His	Asn	Ile	Glu	Asp	Gly	Ser	Val

172 650 Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly Pro 665 Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu Ser 5 680 Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe Val 695 700 Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys 710 10 (2) INFORMATION FOR SEQ ID NO:76: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 2397 base pairs 15 (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: cDNA 20 (ix) FEATURE: (A) NAME/KEY: Coding Sequence (B) LOCATION: 1...2394 (D) OTHER INFORMATION: 25 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:76: ATG GAC AAT ATG TCT ATT ACG AAT ACA CCA ACA AGT AAT GAT GCC TGT Met Asp Asn Met Ser Ile Thr Asn Thr Pro Thr Ser Asn Asp Ala Cys 48 30 10 CTG AGC ATT GTG CAT AGT TTG ATG TGC CAT AGA CAA GGT GGA GAG AGT Leu Ser Ile Val His Ser Leu Met Cys His Arg Gln Gly Glu Ser 96 25 35 GAA ACA TTT GCA AAA AGA GCA ATT GAA AGT TTG GTA AAG AAG CTG AAG Glu Thr Phe Ala Lys Arg Ala Ile Glu Ser Leu Val Lys Lys Leu Lys 144 40 GAG AAA AAA GAT GAA TTG GAT TCT TTA ATA ACA GCT ATA ACT ACA AAT 40 Glu Lys Lys Asp Glu Leu Asp Ser Leu Ile Thr Ala Ile Thr Thr Asn 192 GGA GCT CAT CCT AGT AAA TGT GTT ACC ATA CAG AGA ACA TTG GAT GGG Gly Ala His Pro Ser Lys Cys Val Thr Ile Gln Arg Thr Leu Asp Gly 45 240 AGG CTT CAG GTG GCT GGT CGG AAA GGA TTT CCT CAT GTG ATC TAT GCC Arg Leu Gln Val Ala Gly Arg Lys Gly Phe Pro His Val Ile Tyr Ala 288 50

172

384

CGT CTC TGG AGG TGG CCT GAT CTT CAC AAA AAT GAA CTA AAA CAT GTT
Arg Leu Trp Arg Trp Pro Asp Leu His Lys Asn Glu Leu Lys His Val

AAA TAT TGT CAG TAT GCG TTT GAC TTA AAA TGT GAT AGT GTC TGT GTG

55

										173							
	Lys	Tyr	Cys 115	Gln	Tyr	Ala	Phe	Asp 120	Leu	Lys	Cys	Asp	Ser 125	Val	Cys	Val	
5					TAC Tyr												432
10					CAG Gln												480
15					GAC Asp 165										_	_	528
13					ACC Thr									_			576
20					ACC Thr												624
25					AAC Asn											_	672
30					CTG Leu											_	720
0.5					CAG Gln 245												768
35					CAT His												816
40					ACA Thr												864
45					CCT Pro											_	912
50					GCA Ala												960
					TCC Ser 325												1008
55	GAG	ACA	TTT	AAG	GTT	CCT	TCA	AGC	TGC	CCT	ATT	GTT	ACT	GTT	GAT	GGA	1056

									174							
	Glu	Thr F	he Ly 34	s Val O	Pro	Ser	Ser	Cys 345	Pro	Ile	Val	Thr	Va:		p Gly	
5	-	3	AC CC sp Pr	0 501	GIY (3 3	4sp 360	Arg	Phe	Cys	Leu	Gly 365	Glr	ı Le	u Ser	1104
10	:	370	AC AGO is Aro	,	3	375	iie '	GIU	Arg	Ala	Arg 380	Leu	His	Ile	e Gly	1152
15	385	•	FG CAC	- 20u	390	-ув г	ys (31Υ (31 u (G1y 395	Asp	Val	Trp	Va]	Arg 400	1200
	-		ST GAC	405	nia v	ai P	ne (/al (110 S	Ser	Tyr	Tyr	Leu	Asp 415	Arg	1248
20			G CGT y Arg 420	1114	rio G	IY A	sp 4	11a \ 25	al F	lis :	Lys	Ile	Tyr 430	Pro	Ser	1296
25	GCA T	AT AT yr Il 43	,-	GTC :	Phe A	AT T	eu A	GT C	AG I	GT (His A	CGA Arg 445	CAG Gln	ATG Met	CAG Gln	1344
30	CAG CAG Gln G. 4!	AG GC ln Al	G GCT a Ala	ACT (GCA CA Lla Gl 45	III MI	CT G	CA G la A	CA G la A	la A	GCC (Ala (CAG (Sln)	GCA Ala	GCA Ala	GCC Ala	1392
35	GTG GG Val Al 465			4	70	y PI	O G.	ry S	er V.	al G 75	Sly G	Sly I	lle .	Ala	Pro 480	1440
	GCT AT Ala Il			485	IG AI	a Al	a Gj	LY 1.	le Gi	ly V	al A	sp A	sp i	Leu 195	Arg	1488
40	CGC TT Arg Le	A TGC u Cys	Ile 500	CTC A	GG AT	G AG' t Se:	T TI T Ph 50	ie va	G AA	AA G	GC T ly T	rp G	GA (ly 1	CCG Pro	GAT Asp	1536
45	TAC CC.	A AGA O Arg 515		AGC A	CC AAI le Lys	A GAA s Glu 520	Th	A CC	т то о Су	C TO	rp I	TT G le G 25	AA A lu I	ATT	CAC His	1584
50	TTA CAC Leu His	C CGG B Arg	GCC (CTC CA	AG CTO n Let 535	, пес	A GA As	C GA p Gl	A GT u Va	A CT 1 Le 54	eu H	AT A	CC A	TG (CCG Pro	1632
55	ATT GCA Ile Ala 545	A GAC a Asp	CCA C	CAA CC Sln Pr 55	о пец	A GAC	TG Tr	G GA	T CC. p Pro	o Pr	G GI	CC GC	CC A La T	hr N	ATG Met 560	1680
	GTG AGO	AAG	GGC G	AG GA	G CTG	TTC	ACC	C GGG	G GT	G GT	G CC	C A	יכ כי	TG G	STC	1728

										175							
	Val	Ser	Lys	Gly	Glu 565	Glu	Leu	Phe	Thr	Gly 570	Val	Val	Pro	Ile	Leu 575	Val	
	GAG	CTG	GAC	GGC	GAC	GTA	AAC	GGC	CAC	AAG	TTC	AGC	GTG	TCC	GGC	GAG	1776
5					Asp												
	GGC	GAG	GGC	GAT	GCC	ACC	TAC	GGC	AAG	CTG	ACC	CTG	AAG	TTC	ATC	TGC	1824
					Ala												
10			595					600					605				
					CTG Leu												1872
	1111	610	СТУ	ыyы	Бец	FLO	615	FIO	тър	PIO	1111	620	vai	1111	IIII	Бец	
15												•					
	ACC	TAC	GGC	GTG	CAG	TGC	TTC	AGC	CGC	TAC	CCC	GAC	CAC	ATG	AAG	CAG	1920
		Tyr	Gly	Val	Gln		Phe	Ser	Arg	Tyr		Asp	His	Met	Lys	Gln	
	625					630					635					640	
20	CAC	GAC	ጥጥር	ттс	AAG	TCC	GCC	ልጥር	CCC	CAA	GGC	_Т ъс	стс	CAG	GAG	CGC	1968
20					Lys												1500
		-			645					650	•	•			655		
a.					AAG			-							-		2016
25	Thr	TIE	Pne	660	Lys	Asp	Asp	GIY	Asn 665	туr	гув	unr	Arg	670	GIU	vai	
				000					003					0,0			
	AAG	TTC	GAG	GGC	GAC	ACC	CTG	GTG	AAC	CGC	ATC	GAG	CTG	AAG	GGC	ATC	2064
	Lys	Phe		Gly	Asp	Thr	Leu		Asn	Arg	Ile	Glu		Lys	Gly	Ile	
30			675					680					685				
	GAC	TTC	AAG	GAG	GAC	GGC	AAC	ATC	CTG	GGG	CAC	AAG	CTG	GAG	TAC	AAC	2112
					Asp												
		690	_		_		695			_		700					
35																	
					AAC											_	2160
	705	Asn	ser	HIS	Asn	710	Tyr	ше	Mec	Ата	715	ьуѕ	GIN	гув	Asn	720	
	, 00					, 10					, 13					,20	
40	ATC	AAG	GTG	AAC	TTC	AAG	ATC	CGC	CAC	AAC	ATC	GAG	GAC	GGC	AGC	GTG	2208
	Ile	ГЛЗ	Val	Asn	Phe	Lys	Ile	Arg	His		Ile	Glu	Asp	Gly		Val	
					725					730					735		
	CAG	СТС	GCC	GAC	CAC	TAC	CAG	CAG	AAC	ACC	CCC	АТС	GGC	GAC	GGC	CCC	2256
45					His												
				740	•	_			745				_	750			
					GAC												2304
50	val	ьeu	ьеи 755	PEO	Asp	ASN	HIS	760	ьeu	ser	inr	GIN	5er	ATG	ьeu	ser.	
								. 55					. 55				
	AAA	GAC	CCC	AAC	GAG	AAG	CGC	GAT	CAC	ATG	GTC	CTG	CTG	GAG	TTC	GTG	2352
	Lys	_	Pro	Asn	Glu	Lys	_	Asp	His	Met	Val		Leu	Glu	Phe	Val	
55		770					775					780					
55	ACC	GCC	GCC	GGG	ATC	ACT	СТС	GGC	ΑΤС	GAC	GAG	СТС	TAC	AAG	44 T		2397
										J C	J. 10						1
																	•

176

Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys

5 (2) INFORMATION FOR SEQ ID NO:77:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 798 amino acids
 - (B) TYPE: amino acid
- (C) STRANDEDNESS: single

10

15

- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (v) FRAGMENT TYPE: internal
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:77:

Met Asp Asn Met Ser Ile Thr Asn Thr Pro Thr Ser Asn Asp Ala Cys 5 10 20

Leu Ser Ile Val His Ser Leu Met Cys His Arg Gln Gly Glu Ser 25

Glu Thr Phe Ala Lys Arg Ala Ile Glu Ser Leu Val Lys Lys Leu Lys 40

Glu Lys Lys Asp Glu Leu Asp Ser Leu Ile Thr Ala Ile Thr Thr Asn 25 55 Gly Ala His Pro Ser Lys Cys Val Thr Ile Gln Arg Thr Leu Asp Gly

70 75 Arg Leu Gln Val Ala Gly Arg Lys Gly Phe Pro His Val Ile Tyr Ala

90 30 Arg Leu Trp Arg Trp Pro Asp Leu His Lys Asn Glu Leu Lys His Val 105

Lys Tyr Cys Gln Tyr Ala Phe Asp Leu Lys Cys Asp Ser Val Cys Val 120

Asn Pro Tyr His Tyr Glu Arg Val Val Ser Pro Gly Ile Asp Leu Ser 35 135

140 Gly Leu Thr Leu Gln Ser Asn Ala Pro Ser Ser Met Met Val Lys Asp 150 155

Glu Tyr Val His Asp Phe Glu Gly Gln Pro Ser Leu Ser Thr Glu Gly 165 170

40 His Ser Ile Gln Thr Ile Gln His Pro Pro Ser Asn Arg Ala Ser Thr 185

Glu Thr Tyr Ser Thr Pro Ala Leu Leu Ala Pro Ser Glu Ser Asn Ala 200

Thr Ser Thr Ala Asn Phe Pro Asn Ile Pro Val Ala Ser Thr Ser Gln 45 215 220

Pro Ala Ser Ile Leu Gly Gly Ser His Ser Glu Gly Leu Leu Gln Ile 230 Ala Ser Gly Pro Gln Pro Gly Gln Gln Asn Gly Phe Thr Gly Gln 235

245 Pro Ala Thr Tyr His His Asn Ser Thr Thr Thr Trp Thr Gly Ser Arg 250 50

265 Thr Ala Pro Tyr Thr Pro Asn Leu Pro His His Gln Asn Gly His Leu 280

Gln His His Pro Pro Met Pro Pro His Pro Gly His Tyr Trp Pro Val 55 295 His Asn Glu Leu Ala Phe Gln Pro Pro Ile Ser Asn His Pro Ala Pro

										177						
	305					310					315					320
	Glu	Tyr	Trp	Суз	Ser 325	Ile	Ala	Tyr	Phe	Glu 330	Met	Asp	Val	Gln	Val 335	Gly
5	Glu	Thr	Phe	Lys 340	Val	Pro	Ser	Ser	Cys 345	Pro	Ile	Val	Thr	Val 350	Asp	Gly
	Tyr	Val	Asp 355	Pro	Ser	Gly	Gly	Asp 360	Arg	Phe	Cys	Leu	Gly 365	Gln	Leu	Ser
		370		_			375			_		380		His		-
10	385					390					395			Trp		400
					405					410		_	_	Leu -	415	
15				420					425					Tyr 430		
		-	435	_			_	440	_		_		445	Gln		
20		450					455					460		Ile		
20	465		_			470	_		_		475	_	_	Asp		480
					485				_	490	-		-	Gly	495	_
25	_		_	500		_			505		-	_	_	510 Glu		_
	Leu	His	515 Arg	Ala	Leu	Gln	Leu	520 Leu	Asp	Glu	Val	Leu	525 His	Thr	Met	Pro
30		530 Ala	Asp	Pro	Gln	Pro	535 Leu	Asp	Trp	Asp	Pro	540 Pro	Val	Ala	Thr	Met
	545 Val	Ser	Lys	Gly		550 Glu	Leu	Phe	Thr	-	555 Val	Val	Pro	Ile		560 Val
25	Glu	Leu	Asp		565 Asp	Val	Asn	Gly		570 Lys	Phe	Ser	Val	Ser	575 Gly	Glu
35	Gly	Glu	Gly 595	580 Asp	Ala	Thr	Tyr	Gly 600	585 Lys	Leu	Thr	Leu	Lys 605	590 Phe	Ile	Cys
	Thr	Thr 610		Lys	Leu	Pro	Val 615		Trp	Pro	Thr	Leu 620		Thr	Thr	Leu
40	Thr 625		Gly	Val	Gln	Cys 630		Ser	Arg	Tyr	Pro 635		His	Met	Lys	Gln 640
	His	Asp	Phe	Phe	Lys 645	Ser	Ala	Met	Pro	Glu 650	Gly	Tyr	Val	Gln	Glu 655	Arg
45	•			660		•	-	_	665	_	_			Ala 670		
			675					680					685	Lys		
50	_	690	•		-	-	695			-		700		Glu	-	
50	705					710					715			Lys		720
	_				725					730				Gly	735	
.55				740		_			745				_	Asp 750 Ala	_	
								- 1 -	J-u	DGI					204	

	170	
	755 760 765	
	Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Glu Phe Val	
5	Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys 785 790 795	
	(2) INFORMATION FOR SEQ ID NO:78:	
	(i) SEQUENCE CHARACTERISTICS:	
10	(A) LENGTH: 3138 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single	
	(D) TOPOLOGY: linear	
15	(ii) MOLECULE TYPE: cDNA (ix) FEATURE:	
20	(A) NAME/KEY: Coding Sequence(B) LOCATION: 13135(D) OTHER INFORMATION:	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:78:	
25	ATG GCG GGC TGG ATC CAG GCC CAG CAG CTG CAG GGA GAC GCG CTG CGC Met Ala Gly Trp Ile Gln Ala Gln Gln Leu Gln Gly Asp Ala Leu Arg	48
	1 5 10 15 AFF ATA Lett Arg	
	CAG ATG CAG GTG CTG TAC GGC CAG CAC TTC CCC ATC GAG GTC CGG CAC	
30	20 20 If GIV GIN HIS Phe Pro Ile Glu Val Arg His	96
	25 30	
	TAC TTG GCC CAG TGG ATT GAG AGC CAG CCA TGG GAT GCC ATT GAC TTG	144
35	Tyr Leu Ala Gln Trp Ile Glu Ser Gln Pro Trp Asp Ala Ile Asp Leu 35 40 45	
33	GAC AAT CCC CAG GAC AGA GCC CAA GCC ACG GAG GAG	
	and Alg Ald Gin Ala Thr Gln Leu Clu Clu Clu I-u	192
	55 60	
40	GTG CAG GAG CTG CAG AAG AAG GCG GAG CAC CAG GTG GGG GAA GAT GGG	240
	65 70 75 Ala Giu His Gin Val Gly Glu Asp Gly	240
	75 80	
45	TTT TTA CTG AAG ATC AAG CTG GGG CAC TAC GCC ACG CAG CTC CAG AAA Phe Leu Leu Lys Ile Lys Leu Gly His Tyr Ala Thr Gln Leu Gln Lys	288
	85 90 95	
	ACA TAT GAC CGC TGC CCC CTG GAG CTG GTC CGC TGC ATC CGG CAC ATT	
50	100 Det Git Let Val Arg Cys Ile Arg His Ile	336
	105 110	
	CTG TAC AAT GAA CAG AGG CTG GTC CGA GAA GCC AAC AAT TGC AGC TCT	384
5.E	Leu Tyr Asn Glu Gln Arg Leu Val Arg Glu Ala Asn Asn Cys Ser Ser 115 120 125	
55		
	CCG GCT GGG ATC CTG GTT GAC GCC ATG TCC CAG AAG CAC CTT CAG ATC	432
		178

										179								
	Pro	Ala 130	Gly	Ile	Leu	Val	Asp 135	Ala	Met	Ser	Gln	Lys 140	His	Leu	Gln	Ile		
	AAC	CAG	ACA	TTT	GAG	GAG	CTG	CGA	CTG	GTC	ACG	CAG	GAC	ACA	GAG	AAT	480	
5					Glu										_			
	145					150		_			155		_			160		
	GAG	CTG	AAG	AAA	CTG	CAG	CAG	ACT	CAG	GAG	TAC	TTC	ATC	ATC	CAG	TAC	528	
	Glu	Leu	Lys	Lys	Leu	Gln	Gln	Thr	Gln	${\tt Glu}$	Tyr	Phe	Ile	Ile	Gln	Tyr		
10					165					170					175			
	CAG	GAG	AGC	CTG	AGG	ATC	CAA	GCT	CAG	TTT	GCC	CAG	CTG	GCC	CAG	CTG	576	
	Gln	Glu	Ser		Arg	Ile	Gln	Ala		Phe	Ala	Gln	Leu		Gln	Leu		
15				180					185					190				
13	AGC	CCC	CAG	GAG	CGT	CTG	AGC	CGG	GAG	ACG	GCC	СТС	CAG	CAG	AAG	CAG	624	
					Arg													
			195					200					205		_			
20	GTG	TCT	CTG	GAG	GCC	TGG	TTG	CAG	CGT	GAG	GCA	CAG	ACA	CTG	CAG	CAG	672	
	Val	Ser	Leu	Glu	Ala	\mathtt{Trp}	Leu	Gln	Arg	Glu	Ala	Gln	Thr	Leu	Gln	Gln		
		210					215					220						
	TAC	CGC	GTG	GAG	CTG	GCC	GAG	AAG	CAC	CAG	AAG	ACC	CTG	CAG	CTG	CTG	720	
25	-	Arg	Val	Glu	Leu		Glu	Lys	His	Gln	-	Thr	Leu	Gln	Leu			
	225					230					235					240		
	CGG	AAG	CAG	CAG	ACC	ATC	ATC	CTG	GAT	GAC	GAG	CTG	ATC	CAG	TGG	AAG	768	
00	Arg	Lys	Gln	Gln	Thr	Ile	Ile	Leu	Asp	-	Glu	Leu	Ile	Gln	_	Lys	•	
30					245					250					255			
	CGG	CGG	CAG	CAG	CTG	GCC	GGG	AAC	GGC	GGG	ccc	ccc	GAG	GGC	AGC	CTG	816	
					Leu													
				260					265					270				
35																		
					TCC												864	
	Asp	vai	275	GIII	Ser	пр	Сув	280	ьув	ьeu	AIa	GIU	285	ire	пр	GIII		
			2,3					200					203			•		
40	AAC	CGG	CAG	CAG	ATC	CGC	AGG	GCT	GAG	CAC	CTC	TGC	CAG	CAG	CTG	CCC	912	
	Asn	_	Gln	Gln	Ile	Arg	Arg	Ala	Glu	His	Leu	Cys	Gln	Gln	Leu	Pro		
		290					295					300				•		
	איזיכי	CCC	GGC	CCA	GTG	GAG	GAG	ΔТС	CTG	GCC	GAG	GTC	מממ	GCC	ACC	ልጥሮ	960	
45					Val												200	
	305		-			310					315					320		
					TCA												1008	
50	Thr	Asp	Ile	Ile	Ser	Ala	Leu	Val	Thr		Thr	Phe	Ile	Ile		Lys		
30					325					330					335			
	CAG	ССТ	CCT	CAG	GTC	CTG	AAG	ACC	CAG	ACC	AAG	TTT	GCA	GCC	ACC	GTA	1056	
	Gln	Pro	Pro	Gln	Val	Leu	Lys	Thr	Gln	Thr	Lys	Phe	Ala	Ala	Thr	Val		
				340					345					350				
55	רפת	CTC	CTC	GTC	GGC	GGG	ልአሮ	CTC	ልካሮ	GTC	מאכ	<u>አ</u> ጥሮ	יייתת	ccc	ccc	ርልር	1104	
	CGC	CIG	CIG	GIG	GGC	GGG	MAG	CIG	AAC	GIG	CAC	AIG	AAT	CCC	ccc	CAG	1104	4
																		- 1

	3 .	_							30					
						-	.60				365		Pro Gln	
5	GTG A Val L 3	AG GO ys Al 70	CC AC	C ATC		GT G Ser G	AG C	AG C	AG GC ln Al	CC AAG la Lys 380	TCT	CTG (Leu L	CTT AAA Leu Lys	1152
10	AAT G. Asn G. 385	AG AA lu As	AC ACC	C CGC Arg	AAC G Asn G 390	AG T	GC A	GT G er G	GT GA ly Gl 39	u Ile	CTG .	AAC A Asn A	AC TGC sn Cys	1200
15	TGC G Cys Va	TG AT al Me	G GAG	TAC Tyr 405	CAC C His G	AA G	CC AC	CG GC nr G] 41	Ly Th	C CTC r Leu	AGT (Ala H	AC TTC is Phe 15	1248
	AGG AA Arg As	AC ATO	G TCA t Ser 420	CTG Leu	AAG A Lys A	GG A1	C AA le Ly 42	B Ar	GT GC	T GAC a Asp	Arg P	CGG GC Arg GI	GT GCA ly Ala	1296
20	GAG TO Glu Se	C GT(r Va] 435	G ACA l Thr	GAG (GAG AA Glu L	AG TI VS Ph 44	e in	A GT r Va	C CTC	ı Phe	GAG I Glu S 445	CT CA	AG TTC	1344
25	AGT GT Ser Va 45	T GGC l Gly 0	C AGC Ser	AAT (GAG CT Glu Le 45	u va	G TT 1 Ph	C CA	G GTG n Val	AAG Lys 460	ACT C	TG TC	C CTA	1392
30	CCT GTO Pro Val 465	G GTT l Val	GTC Val		TC CA al Hi 70	C GG	C AGO	C CAC	G GAC n Asp 475	CAC A	AAT G Asn A	CC AC la Th	G GCT r Ala 480	1440
35	ACT GTO	CTG Leu	TGG Trp	GAC A Asp A 485	AT GC	C TT:	Γ GC7 ⊇ Ala	GAG Glu 490	Pro	GGC A	AGG G: Arg Va	rg cca al Pro 499	> Phe	1488
	GCC GTG Ala Val	CCT Pro	GAC Asp 500	AAA G Lys V	TG CTO	TGG Trp	CCG Pro 505	Gln	CTG Leu	TGT G	AG GC lu Al 51	a Leu	C AAC 1 Asn	1536
40	ATG AAA Met Lys	TTC Phe 515	AAG (GCC GA	AA GTO	G CAG Gln 520	ser	AAC Asn	CGG Arg	Gly L	TG AC eu Th 25	C AAG	GAG Glu	1584
45	AAC CTC Asn Leu 530	GTG Val	TTC (CTG G(eu Al	CG CAG a Gln 535	цуѕ	CTG Leu	TTC Phe	Asn	AAC AG Asn So	GC AG er Se	C AGC r Ser	CAC	1632
50	CTG GAG Leu Glu 545	GAC Asp	TAC A	GT GG er Gl 55	y neu	TCC Ser	GTG Val	TCC Ser	TGG Trp 555	TCC CA	AG TTO	C AAC e Asn	AGG Arg 560	1680
55	GAG AAC Glu Asn	TTG (GC TG ly Tr 65	G AAC p Asn	TAC Tyr	ACC Thr	TTC Phe 570	TGG (CAG TO	G TTT	GAC Asp 575	GGG Gly	1728
	GTG ATG	GAG (GTG T	TG AA	G AAG	CAC	CAC	AAG	ccc (CAC TG	TAA D	GAT	GGG	1776 180

										181							
	Val	Met	Glu	Val 580	Leu	Lys	Lys	His	His 585	Lys	Pro	His	Trp	Asn 590	Asp	Gly	
5				GGT Gly													1824
10				GAC Asp													1872
15				ACC Thr													1920
				AAA Lys													1968
20	_			CTG Leu 660	_												2016
25				GAT Asp													2064
30				GAT Asp													2112
35				AAT Asn													2160
55				GCC Ala													2208
40				CAG Gln 740													2256
45				GAG Glu													2304
50				ATG Met													2352
55				TCT Ser													2400
00,	GAT	CCA	CCG	GTC	GCC	ACC	ATG	GTG	AGC	AAG	GGC	GAG	GAG	CTG	TTC	ACC	2448

	182	
	Asp Pro Pro Val Ala Thr Met Val Ser Lys Gly Glu Glu Leu Phe Thr 805 810 815	
5	GGG GTG GTG CCC ATC CTG GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC Gly Val Val Pro Ile Leu Val Glu Leu Asp Gly Asp Val Asn Gly His 820 825 830	2496
10	AAG TTC AGC GTG TCC GGC GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG Lys Phe Ser Val Ser Gly Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys 835 840 845	2544
15	CTG ACC CTG AAG TTC ATC TGC ACC ACC GGC AAG CTG CCC GTG CCC TGG Leu Thr Leu Lys Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro Trp 850 855 860	2592
20	CCC ACC CTC GTG ACC ACC CTG ACC TAC GGC GTG CAG TGC TTC AGC CGC Pro Thr Leu Val Thr Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg 865 870 875 880	2640
20	TAC CCC GAC CAC ATG AAG CAG CAC GAC TTC TTC AAG TCC GCC ATG CCC Tyr Pro Asp His Met Lys Gln His Asp Phe Phe Lys Ser Ala Met Pro 885 890 895	2688
25	GAA GGC TAC GTC CAG GAG CGC ACC ATC TTC TTC AAG GAC GAC GGC AAC Glu Gly Tyr Val Gln Glu Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn 900 905 910	2736
30	TAC AAG ACC CGC GCC GAG GTG AAG TTC GAG GGC GAC ACC CTG GTG AAC Tyr Lys Thr Arg Ala Glu Val Lys Phe Glu Gly Asp Thr Leu Val Asn 915 920 925	2784
35	CGC ATC GAG CTG AAG GGC ATC GAC TTC AAG GAG GAC GGC AAC ATC CTG Arg Ile Glu Leu Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu 930 940	2832
	GGG CAC AAG CTG GAG TAC AAC TAC AAC AGC CAC AAC GTC TAT ATC ATG Gly His Lys Leu Glu Tyr Asn Tyr Asn Ser His Asn Val Tyr Ile Met 950 955 960	2880
40	GCC GAC AAG CAG AAG AAC GGC ATC AAG GTG AAC TTC AAG ATC CGC CAC Ala Asp Lys Gln Lys Asn Gly Ile Lys Val Asn Phe Lys Ile Arg His 965 970 975	2928
45	AAC ATC GAG GAC GGC AGC GTG CAG CTC GCC GAC CAC TAC CAG CAG AAC Asn Ile Glu Asp Gly Ser Val Gln Leu Ala Asp His Tyr Gln Gln Asn 980 985 990	2976
50	ACC CCC ATC GGC GAC GGC CCC GTG CTG CTG CCC GAC AAC CAC TAC CTG Thr Pro Ile Gly Asp Gly Pro Val Leu Leu Pro Asp Asn His Tyr Leu 995 1000 1005	3024
55	AGC ACC CAG TCC GCC CTG AGC AAA GAC CCC AAC GAG AAG CGC GAT CAC Ser Thr Gln Ser Ala Leu Ser Lys Asp Pro Asn Glu Lys Arg Asp His 1010 1015 1020	3072
	ATG GTC CTG GAG TTC GTG ACC GCC GCC GGG ATC ACT CTC GGC ATG	3120 182

183

Met Val Leu Leu Glu Phe Val Thr Ala Ala Gly Ile Thr Leu Gly Met 1025 1030 1035 1040

GAC GAG CTG TAC AAG TAA
5 Asp Glu Leu Tyr Lys

3138

(2) INFORMATION FOR SEQ ID NO:79:

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- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 1045 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
- 15 (D) TOPOLOGY: linear
 - (ii) MOLECULE TYPE: protein
 - (v) FRAGMENT TYPE: internal
- 20 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:79:

Met Ala Gly Trp Ile Gln Ala Gln Gln Leu Gln Gly Asp Ala Leu Arg

1 5 10 15

Gln Met Gln Val Leu Tyr Gly Gln His Phe Pro Ile Glu Val Arg His 25 25 30

25 20 25 30 Tyr Leu Ala Gln Trp Ile Glu Ser Gln Pro Trp Asp Ala Ile Asp Leu

35 40 45

Asp Asn Pro Gln Asp Arg Ala Gln Ala Thr Gln Leu Glu Gly Leu
50 55 60

30 Val Gln Glu Leu Gln Lys Lys Ala Glu His Gln Val Gly Glu Asp Gly 65 70 75 80

Phe Leu Leu Lys Ile Lys Leu Gly His Tyr Ala Thr Gln Leu Gln Lys

85 90 95
Thr Tyr Asp Arg Cys Pro Leu Glu Leu Val Arg Cys Ile Arg His Ile

35 100 105 110 Leu Tyr Asn Glu Gln Arg Leu Val Arg Glu Ala Asn Asn Cys Ser Ser 115 120 125

Pro Ala Gly Ile Leu Val Asp Ala Met Ser Gln Lys His Leu Gln Ile
130 135 140

Asn Gln Thr Phe Glu Glu Leu Arg Leu Val Thr Gln Asp Thr Glu Asn 145 150 155 160

Glu Leu Lys Lys Leu Gln Gln Thr Gln Glu Tyr Phe Ile Ile Gln Tyr
165 170 175

Gln Glu Ser Leu Arg Ile Gln Ala Gln Phe Ala Gln Leu Ala Gln Leu 45 180 185 190

Ser Pro Gln Glu Arg Leu Ser Arg Glu Thr Ala Leu Gln Gln Lys Gln 195 200 205

Val Ser Leu Glu Ala Trp Leu Gln Arg Glu Ala Gln Thr Leu Gln Gln 210 220

Tyr Arg Val Glu Leu Ala Glu Lys His Gln Lys Thr Leu Gln Leu Leu 225 230 235 240 Arg Lys Gln Gln Thr Ile Ile Leu Asp Asp Glu Leu Ile Gln Trp Lys

245 250 255
Arg Arg Gln Gln Leu Ala Gly Asn Gly Gly Pro Pro Glu Gly Ser Leu

Arg Arg Gin Gin hed Ara Gly Ash Gly Gly Pro Gid Gly Ser hed

55 260 265 270

Asp Val Leu Gln Ser Trp Cys Glu Lys Leu Ala Glu Ile Ile Trp Gln

275 Asn Arg Gln Gln Ile Arg Arg Ala Glu His Leu Cys Gln Gln Leu Pro 290 11e Pro Gly Pro Val Glu Glu Met Leu Ala Glu Val Asn Ala Thr Ile 310 315 316 Thr Asp Ile Ile Ser Ala Leu Val Thr Ser Thr Phe Ile Ile Glu Lys 325 330 Gln Pro Pro Gln Val Leu Lys Thr Gln Thr Lys Phe Ala Ala Thr Val 325 340 345 346 357 348 Asn Ala Gly Gly Lys Leu Asn Val His Met Asn Pro Pro Gln 355 360 375 380 Asn Glu Asn Thr Ile Ile Ser Glu Gln Gln Ala Lys Ser Leu Leu Lys 370 Asn Glu Asn Thr Arg Asn Glu Cys Ser Gly Glu Ile Leu Asn Asn Arg 370 Asn Glu Asn Thr Arg Asn Glu Cys Ser Gly Glu Ile Leu Asn Asn Cys 385 Asn Glu Asn Thr Arg Asn Glu Cys Ser Gly Glu Ile Leu Asn Asn Cys 385 Asn Glu Asn Thr Arg Asn Glu Cys Ser Gly Glu Ile Leu Asn Asn Cys 385 Asn Glu Asn Thr Arg Asn Glu Cys Ser Gly Glu Ile Leu Asn Asn Cys 385 Asn Glu Asn Thr Glu Glu Lys Phe Thr Val Leu Phe Glu Ser Gln Phe 405 Arg Asn Met Ser Leu Lys Arg Ile Lys Arg Ala Asp Arg Arg Gly Ala 420 Glu Ser Val Thr Glu Glu Lys Phe Thr Val Leu Phe Glu Ser Gln Phe 435 Asn Cal Val Val Val Ile Val Phe Gln Val Lys Thr Leu Ser Leu 445 Pro Val Val Val Ile Val His Gly Ser Gln Asp His Asn Ala Thr Ala 450 Asn Leu Trp Asp Asn Ala Phe Ala Glu Pro Gly Arg Val Pro Phe 485 Ala Val Pro Asp Lys Val Leu Trp Pro Gln Leu Cys Glu Ala Leu Asn 500 Met Lys Phe Lys Ala Glu Val Gln Ser Asn Arg Gly Leu Thr Lys Glu 515 Asn Leu Val Phe Leu Ala Gln Lys Leu Phe Asn Asn Ser Ser Ser His 516 Asn Leu Val Phe Leu Ala Gln Lys Leu Phe Asn Asn Arg Gly Leu Thr Lys Glu 517 Asn Leu Val Phe Leu Ala Gln Lys Leu Phe Asn Asn Arg Gly Leu Thr Lys Glu 518 Asn Leu Val Phe Leu Ala Gln Lys Leu Phe Asn Asn Arg Gly Leu Thr Lys Glu 519 Asn Leu Glu Asp Tyr Ser Gly Leu Ser Val Ser Trp Ser Gln Phe Asn Arg 510 Asn Leu Val Phe Leu Ala Gln Lys Leu Phe Asn Asn Arg Gly Leu Thr Lys Glu 515 520 Asn Leu Glu Asp Tyr Ser Gly Leu Ser Val Ser Trp Ser Gln Phe Asn Arg 610 Asn Leu Gly Phe Val Asn Lys Gln Gln Ala His Asp Leu Leu Ile 610 Asn Lys Pro Asp Gly Thr Phe Leu Leu Arg Phe Ser Asp Ser Glu Ile 610 Gly Gly Ile Thr I e Ala Trp L													•	184								
11		_			275	i					28	0						205	,			
11e Pro Gly Pro Val Glu Glu Met Leu Ala Glu Val Asn Ala Thr Ile 5		A	sn i	Arg 290	Glr	Gl	n I	le A	rg A	Arg	Al	a G	lu	His	s Le	eu ('ys	Gln	G]	n L	eu	Pro
Thr Asp Ile Ile Ser Ala Leu Val Thr Ser Thr Phe Ile Ile Glu Lys 325 335 335 336 335 336 346	_	Ι	le 1	Pro	Gly	Pr	o Va	al G	lu c	lu	Me	t Le	eu	Ala	a G1	tin ti	00 'al	λαη	וה	- m	.	
Sin Pro Pro Sin Val Leu Lys Thr Sin Thr Lys Phe Ala Ala Thr Val	5	3	05 b= 7					3	10						31	15	uı	nau	. AI	d 1	nr	TTE
Sin Pro Pro Gin Val Leu Lys Thr Gin Thr Lys Phe Ala Ala Thr Val 340		1,1	-	asp	тте	11	e Se 32	er A 25	la I	eu	Va:	l Tì	ır	Ser 330	Th	ır P	he	Ile	11	e G	lu	Lys
Arg Leu Leu Val Gly Gly Lys Leu Asn Val His Met Asn Pro Pro Gln 155 360 360 365 360 370 370 370 375 380 370 375 380 370 375 380 370 375 380 385 390 395 400 415 420 425 425 425 426 436 436 426 436 436 436 445 436 445													n'	Thr	. Г							
Val Lys Ala Thr IIe 11e Ser Glu Gln Ala Lys Ser Leu Leu Leu Lys 375 380 380 380 Asn Leu Asn	10											ı As	n '									
Asn Glu Asn Thr Arg Asn Glu Cys Ser Gly Glu Ile Leu Asn Asn Cys 390		Va	al L 3	ys 70	Ala	Thi	r Il	e II	le S	er	Glu	, Gl	n (31n	Al	a L	ys .	365 Ser	Le	u Le	eu	Lys
Cys Val Met Glu Tyr His Gln Ala Thr Gly Thr Leu Ser Ala His Phe	4-	As	n G	lu .	Asn	Thi	Ar	g As	n G	lu	Cvs	Se	r (:lv	G1	3: T	80 10 :					
Cys Val Met Glu Tyr His Gln Ala Thr Gly Thr Leu Ser Ala His Phe	15	38	15	_				39	0		-1-			-	39	u 1. 5	re .	Leu	Ası	n As	n	Cys
Arg Asn Met Ser Leu Lys Arg I1e Lys Arg Ala Asp Arg Arg Ala Asp Arg		Су	s V	al)	Met	Glu	1 Ty:	r Hi 5	s G	ln .	Ala	Th	r (Sly	Th	r Le	eu s	Ser	Ala	a Hi	s :	Phe
Ser Val Thr Glu Glu Lys Phe Ato Add		Ar	g A	sn 1	Met	Ser 420	Le	u Ly	s Aı	g	Ile	Ly.	s A	rg	Ala	a As	sp A	۱rg	Arg	g Gl	5 У <i>і</i>	Ala
Ser Val Gly Ser Asn Glu Leu Val Phe Gln Val Lys Thr Leu Ser Leu	20											Th	r V									
Pro		Se	r Va 45	al (50	Sly	Ser	Ası	ı Gl	u Le	u V	/al	Phe	∍ G	ln	Va]	Lц	s I	hr	Leu	Se	r I	eu
Thr Val Leu Trp Asp	25	Pro 46!	0 Vá 5	al V	/al	Val	Ile	Va:	l Hi	s (Sly	Sei	G	ln	Asp) Hi	o s A	sn.	Ala	Th	r A	la
Ala Val Pro		Th	r Va	l L	eu	Trp	Asp	Ası	a Al	a F	he	Ala	G.	lu	475 Pro	G1	уА	rg '	Val	Pro	4 > P	80 he
Met Lys Phe Lys Ala Glu Val Gln Ser Asn Arg Gly Leu Thr Lys Glu		Ala	a Va	1 P	ro .	qaA	Lys	Va]	l Le	u 7	rp	Pro	G.	90 ln :	Leu	Су	s G	lu i	Ala	495 Let	5 1 A	sn
Ash Leu Val Phe Leu Ala Gln Lys Leu Phe Ash Ser Ser Ser His Say Leu Glu Ash Tyr Ser Gly Leu Ser	30									1 G	ln											
Leu Glu Asp Tyr Ser Gly Leu Ser Val Ser Trp Ser Gln Phe Asp Arg 545 545 550 550 550 550 570									Gli	пЪ												
Simple S	35	Leu 545	Gl	u A:	sp 1	ſуr	Ser	Gly	Lei	ıs	er	Val	Se	er T	Гrр	540 Sea) : G]	ln F	he	Asn	. A:	ra
Val Met Glu Val Leu Lys Lys His His Lys Pro His Try Asn Asp Gly 590 Ala Ile Leu Gly Phe Val Asn Lys Glo Glo Gln Ala His Asp Leu Leu Ile 605 Asn Lys Pro Asp Gly Thr Phe Leu Leu Arg Phe Ser Asp Ser Glu Ile 610 Gly Gly Ile Thr Ile Ala Trp Lys Phe Asp Ser Glo Asp Glo Glo Glo Glo Glo Glo Glo Glo Glo Arg Asp Leu Glo Glo Glo Glo Arg Asp Leu Glo Glo Glo Glo Glo Arg Asp Leu Glo Glo Glo Glo Arg Asp Leu Glo Glo Glo Glo Glo Glo Arg Asp Leu Glo Glo Glo Glo Glo Glo Arg Asp Leu Glo		Glu	Ası	n Le	eu F	ro	Gly	Trp	Asr	1 T	yr	Thr	Ph	e 7	555 Crp	Glr	ı Tr	p F	he	Asp	56 G:	50 lv
40 Ala Ile Leu Gly Phe Val Asn Lys Gln Gln Ala His Asp Leu Leu Ile 595		Val	Met	G]	lu V	al	Leu	Lys	Lys	: Н:	is 1	His	57 Ly	o s F	Pro	His	Tr	no A	sn	575 Asp	G]	-ı Lv
Asn Lys Pro Asp Gly Thr Phe Leu Leu Arg Phe Ser Asp Ser Glu Ile 610	40	Ala	Ιlε	≥ Le	eu G	lv	Phe	Val	λαπ	т.	!	585	~1	_				5	90		_	- 7
Gly Gly Ile Thr Ile Ala Trp Lys Phe Asp Ser Pro Glu Arg Asn Leu 625																						
Trp Asn Leu Lys Pro Phe Thr Thr Arg Asp Phe Ser Ile Arg Ser Leu 645 Ala Asp Arg Leu Gly Asp Leu Ser Tyr Leu Ile Tyr Val Phe Pro Asp 665 Arg Pro Lys Asp Glu Val Phe Ser Lys Tyr Tyr Thr Pro Val Leu Ala 675 Lys Ala Val Asp Gly Tyr Val Lys Pro Gln Ile Lys Gln Val Pro 690 Glu Phe Val Asn Ala Ser Ala Asp Ala Gly Gly Ser Ser Ala Thr Tyr		Glv	610 Glv	. Tl	е Т	hr	T10	771	615	_ ⊾∈	eu 1	Leu	Ar	g P	he	Ser 620	As	p S	er	Glu	11	.e
50 Arg Pro Lys Asp Glu Val Phe Ser Lys Tyr Tyr Thr Pro Val Leu Ala 675 Lys Ala Val Asp Gly Tyr Val Lys Pro 685 Lys Ala Val Asp Gly Tyr Val Lys Pro 685 Glu Phe Val Asn Ala Ser 710 The Arg Asp Phe Ser Ile Arg Ser Leu 655 Tyr Leu Ile Tyr Val Phe Pro Asp 670 Tyr Tyr Tyr Tyr Thr Pro Val Leu Ala 685 From 695 Glu Phe Val Asn Ala Ser Ala Asp Ala Gly Gly Ser Ser Ala Thr Tyr	45																					
Ala Asp Arg Leu Gly Asp Leu Ser Tyr Leu Ile Tyr Val Phe Pro Asp 660		Trp	Asn	Le	u L	ys 1	Pro 545	Phe	Thr	Th	r P	Arg	Ası	P.	he	Ser	11	e A	rg i	Ser	64 Le	o u
Arg Pro Lys Asp Glu Val Phe Ser Lys Tyr Tyr Thr Pro Val Leu Ala 675 680 685 Lys Ala Val Asp Gly Tyr Val Lys Pro Gln Ile Lys Gln Val Val Pro 690 690 695 700 695 705 710													Leı	ı I.								
Lys Ala Val Asp Gly Tyr Val Lys Pro Gln Ile Lys Gln Val Val Pro Glu Phe Val Asn Ala Ser Ala Asp Ala Gly Gly Ser Ser Ala Thr Tyr 710	50	Arg	Pro	Ly:	s As 5	sp G	3lu	Val	Phe	Se	r L	ys	Туг	T	yr	Thr	Pro	67 5 Va	70 al 1	Ĺeu	Al.	a
Glu Phe Val Asn Ala Ser Ala Asp Ala Gly Gly Ser Ser Ala Thr Tyr 700 710		Lys	Ala 690	Va:	l As	sp G	ly '	Tyr	Val 695	Lу	s P	ro	Gln	ı I.	le :	Lys	Glr	ı Va	11 1	/al	Pro	ɔ
Met Asp Gln Ala Pro Ser Pro Ala Val Cys Pro Gln Ala Pro Tyr Asn		Glu 705	Phe	Va]	l As	n A	las	Ser 710	Ala	As	PΑ	la	Gly	G]	ly s	Ser	Ser	Al	.a 1	hr	Туз	r
		Met .	Asp	Glr	ı Al	a P	ro s	Ser	Pro	Ala	a V	al (Cys	Pr	:0 (Gln	Ala	Pr	r o	yr .	72(Asr) 1

185

					725					730					735	
	Met	Tyr	Pro	Gln 740	Asn	Pro	Asp	His	Val 745	Leu	Asp	Gln	Asp	Gly 750	Glu	Ph∈
5	Asp	Leu	Asp 755	Glu	Thr	Met	Asp	Val 760	Ala	Arg	His	Val	Glu 765	Glu	Leu	Lev
•	Arg			Met	Asp	Ser			Ser	Arg	Leu			Pro	Ala	Gly
	Leu	770 Phe	Thr	Ser	Ala	Arg	775 Gly	Ser	Leu	Ser	Trp	780 Val	Pro	Arg	Ala	Arg
	785					790					795					800
10	Asp	Pro	Pro	Val	Ala 805	Thr	Met	Val	Ser	Lys 810	Gly	Glu	Glu	Leu	Phe 815	Thr
	Gly	Val	Val	Pro 820	Ile	Leu	Val	Glu	Leu 825	Asp	Gly	Asp	Val	Asn 830	Gly	His
15	Lys	Phe	Ser 835	Val	Ser	Gly	Glu	Gly 840	Glu	Gly	Asp	Ala	Thr 845	Tyr	Gly	Lys
	Leu	Thr 850	Leu	Lys	Phe	Ile	Cys 855	Thr	Thr	Gly	Lys	Leu 860		Val	Pro	Trp
	Pro 865	Thr	Leu	Val	Thr	Thr 870	Leu	Thr	Tyr	Gly	Val 875		Сув	Phe	Ser	Arg
20		Pro	Asp	His	Met 885		Gln	His	Asp	Phe 890	_	Lys	Ser	Ala	Met 895	
	Glu	Glý	Tyr	Val 900		Glu	Arg	Thr	Ile 905		Phe	Lys	Asp	Asp 910		Asn
25	Tyr	Lys	Thr 915	Arg	Ala	Glu	Val	Lys 920		Glu	Gly	Asp	Thr 925		Val	Asn
	Arg	Ile 930		Leu	Lys	Gly	Ile 935		Phe	Lys	Glu	Asp 940		Asn	Ile	Leu
	Gly 945		Lys	Leu	Glu	Tyr 950		Tyr	Asn	Ser	His 955		Val	Tyr	Ile	Met
30		Asp	Lys	Gln	Lys 965		Gly	Ile	Lys	Val 970		Phe	Lys	Ile	Arg 975	
	Asn	Ile	Glu	Asp 980		Ser	Val	Gln	Leu 985		Asp	His	Tyr	Gln 990		Asn
35	Thr	Pro	Ile 995	Gly	Asp	Gly		Val		Leu	Pro		Asn		Tyr	Leu
	Ser	Thr		Ser	Ala	Leu			Asp	Pro	Asn			Arg	Asp	His
		1010					1015	-	-			1020	•	_	•	
		Val	Leu	Leu			Val	Thr	Ala			Ile	Thr	Leu		
40	025 Asp	Glu	Leu	Tyr		L030					1035					1040
				-	1045											
			(2)	INI	FORM	OITA	V FOI	R SE	Q ID	NO:	30:					
45		(i		EQUE												

- - (B) TYPE: nucleic acid

 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

50

55

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:80:

TGGGATCCTC AGGCCGTGCT GCTGGCCG

(2) INFORMATION FOR SEQ ID NO:81:

185

5	 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 27 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 	
10	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:81: GTCTCGAGGG AGCATGGGCA CCTTGCG	
15	(2) INFORMATION FOR SEQ ID NO:82:(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 27 base pairs	2
20	(B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear	
25	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:82: TGGGATCCGA GAAGTCTATA TCCCATC (2) INFORMATION FOR SEQ ID NO:83:	27
30	(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 28 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear	
35	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:83:	
40	TGGGATCCTT AGAAGTCTAT ATCCCATC (2) INFORMATION FOR SEQ ID NO:84: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 28 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear	28
50	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:84: GTCTCGAGCC ATGAACGCCC CCGAGCGG (2) INFORMATION FOR SEQ ID NO:85:	28
55	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 30 base pairs(B) TYPE: nucleic acid	

187

	(C) STRANDEDNESS: single (D) TOPOLOGY: linear	
5	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:85:	
	GTGAATTCTC GTCTGATTTC TGGCAGGAGG	30
10	(2) INFORMATION FOR SEQ ID NO:86:	
15	 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 30 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:86:	
20	GTGAATTCTT TACGTCTGAT TTCTGGCAGG	30
	(2) INFORMATION FOR SEQ ID NO:87:	
25	(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 34 base pairs (B) TYPE: nucleic acid	
	(C) STRANDEDNESS: single (D) TOPOLOGY: linear	
30	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:87:	
	GTCTCGAGCC ATGGACGAAC TGTTCCCCCT CATC	34
35	(2) INFORMATION FOR SEQ ID NO:88:	
	(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 31 base pairs	
40	(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear	
45	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:88:	
.0	GTGGATCCAA GGAGCTGATC TGACTCAGCA G	31
	(2) INFORMATION FOR SEQ ID NO:89:	
50	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 32 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single	

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(D) TOPOLOGY: linear

	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:89:	
	GTGGATCCTT AGGAGCTGAT CTGACTCAGC AG	32
5	(2) INFORMATION FOR SEQ ID NO:90:	
10	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 32 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear	
15	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:90:	
	CCTCCTAAGC TTATCATGGA CCATTATGAT TC	32
	(2) INFORMATION FOR SEQ ID NO:91:	
20	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 33 base pairs(B) TYPE: nucleic acid	
25	(C) STRANDEDNESS: single (D) TOPOLOGY: linear	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:91:	
30	CCTCCTGGAT CCCTGCGCAG GATGATGGTC CAG	33
	(2) INFORMATION FOR SEQ ID NO:92:	
35	(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 45 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear	
40	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:92:	
	GGATGGAAGC TTCAATGGCT GCCATCCGGA AGAAACTGGT GATTG	45
45	(2) INFORMATION FOR SEQ ID NO:93:	.,
	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 45 base pairs(B) TYPE: nucleic acid	
50	(C) STRANDEDNESS: single (D) TOPOLOGY: linear	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:93:	
55	GGATGGGGAT CCTCACAAGA CAAGGCAACC AGATTTTTC TTCCC	45

	189	
	(2) INFORMATION FOR SEQ ID NO:94:	
5	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 29 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear	
10	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:94:	
	GGGAAGCTTC CATGAGCGAG ACGGTCATC	29
15	(2) INFORMATION FOR SEQ ID NO:95:	
	(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 28 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single	
20	(D) TOPOLOGY: linear	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:95:	
25	CCCGGATCCT CAGGGAGAAC CCCGCTTC	28
	(2) INFORMATION FOR SEQ ID NO:96:	
30	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 30 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear	
35		
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:96:	2.0
40	GTGAATTCGA CCATGGAGCG GCCCCCGGGG	30
40	(2) INFORMATION FOR SEQ ID NO:97:	
-	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 27 base pairs(B) TYPE: nucleic acid	
45	<pre>(C) STRANDEDNESS: single (D) TOPOLOGY: linear</pre>	
50	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:97:	
	GTGGTACCCA TTCTGTTAAC CAACTCC	27
•	(2) INFORMATION FOR SEQ ID NO:98:	
55	(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 28 base pairs	

	190	
	(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear	
5		
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:98:	
	GTGGTACCTC ATTCTGTTAA CCAACTCC	28
10	(2) INFORMATION FOR SEQ ID NO:99:	
15	 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 28 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 	
20	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:99:	
	GTCTCGAGAG ATGCTGTCCC GTGGGTGG	28
	(2) INFORMATION FOR SEQ ID NO:100:	
25	(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 27 base pairs	
30	(B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:100:	
35	GTGAATTCGC TTCCTCTTGA GGGAACC	27
	(2) INFORMATION FOR SEQ ID NO:101:	
40	 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 27 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 	
45	(vi) apovenia	
,,,	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:101:	
	GTGAATTCAC TTCCTCTTGA GGGAACC	27
50	(2) INFORMATION FOR SEQ ID NO:102:	
	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 29 base pairs	
	(B) TYPE: nucleic acid	
55	(C) STRANDEDNESS: single (D) TOPOLOGY: linear	

	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:102:	
E	GTCTCGAGCC ATGGAGAACT TCCAAAAGG	29
5	(2) INFORMATION FOR SEQ ID NO:103:	
	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 28 base pairs	
10	(B) TYPE: nucleic acid (C) STRANDEDNESS: single	
	(D) TOPOLOGY: linear	
15	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:103:	
	GTGGATCCCA GAGTCGAAGA TGGGGTAC	28
20	(2) INFORMATION FOR SEQ ID NO:104:	
	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 29 base pairs(B) TYPE: nucleic acid	
	(C) STRANDEDNESS: single	
25	(D) TOPOLOGY: linear	•
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:104:	
30	GTGGATCCTC AGAGTCGAAG ATGGGGTAC	29
	(2) INFORMATION FOR SEQ ID NO:105:	
	(i) SEQUENCE CHARACTERISTICS:	
35	(A) LENGTH: 30 base pairs	
	(B) TYPE: nucleic acid (C) STRANDEDNESS: single	
	(D) TOPOLOGY: linear	
40	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:105:	
	GTGAATTCGG CGATGCCAGA CCCCGCGGCG	30
45	(2) INFORMATION FOR SEQ ID NO:106:	
	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 32 base pairs(B) TYPE: nucleic acid	
50	(C) STRANDEDNESS: single	
	(D) TOPOLOGY: linear	
55	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:106:	
JJ	GTGGATCCCA GGCACAGGCA GCCTCAGCCT TC	32
		191

	(2) INFORMATION FOR SEQ ID NO:107:	
5	 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 33 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 	
10		
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:107:	
	GTGGATCCTC AGGCACAGGC AGCCTCAGCC TTC	33
15	(2) INFORMATION FOR SEQ ID NO:108:	
20	 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 2616 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 	
25	(ii) MOLECULE TYPE: cDNA(ix) FEATURE:(A) NAME/KEY: Coding Sequence	
	(B) LOCATION: 12613 (D) OTHER INFORMATION:	
30	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:108:	
	ATG GTG AGC AAG GGC GAG GAG CTG TTG AGG GTG	
35	Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu 1 10 15	48
	GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 25	96
40	GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile 35	144
45	TGC ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr 50 55 60	192
50	CTG ACC TAC GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG AAG Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys 65 70 75 80	240
55	CAG CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu 85 90 95	288
	CGC ACC ATC TTC TTC AAG GAC GAC GGC AAC TAC AAG ACC CGC GCC GAG	336 192

										193								
	Arg	Thr	Ile	Phe 100	Phe	Lys	Asp	Asp	Gly 105	Asn	Tyr	Lys	Thr	Arg 110	Ala	Glu		
5					GGC Gly												384	4
10					GAG Glu												432	2
15					CAC His		_										486	0
					AAC Asn 165												528	3
20					GAC Asp												576	5
25		_			CCC Pro												624	1
30					AAC Asn												672	2
35					GGG Gly												720	ס
	_				CGA Arg 245	_											76	8
40		_			CCC Pro												81	5
45					AAG Lys												864	4
50					CGC Arg												91:	2
55					CAC His												960	0
55	TAC	GCC	ATT	GCC	GGC	GGC	AAA	GCG	CAC	TGT	GGA	CCG	GCA	GAG	CTC	TGC	100	B 1

	194
	Tyr Ala Ile Ala Gly Gly Lys Ala His Cys Gly Pro Ala Glu Leu Cys 325 330 335
:	GAG TTC TAC TCG CGC GAC CCC GAC GGG CTG CCC TGC AAC CTG CGC AAG 1056 Glu Phe Tyr Ser Arg Asp Pro Asp Gly Leu Pro Cys Asn Leu Arg Lys 340 345 350
10	360 365
15	- •
20	CTG GAG GGC GAG GCC CTG GAG CAG GCC ATC ATC AGC CAG GCC CCG CAG Leu Glu Gly Glu Ala Leu Glu Gln Ala Ile Ile Ser Gln Ala Pro Gln 385 390 395 400
20	GTG GAG AAG CTC ATT GCT ACG ACG GCC CAC GAG CGG ATG CCC TGG TAC Val Glu Lys Leu Ile Ala Thr Thr Ala His Glu Arg Met Pro Trp Tyr 405 410 415
25	CAC AGC AGC CTG ACG CGT GAG GAG GCC GAG CGC AAA CTT TAC TCT GGG His Ser Ser Leu Thr Arg Glu Glu Ala Glu Arg Lys Leu Tyr Ser Gly 420 425 430
30	GCG CAG ACC GAC GGC AAG TTC CTG CTG AGG CCG CGG AAG GAG CAG GGC 1344 Ala Gln Thr Asp Gly Lys Phe Leu Leu Arg Pro Arg Lys Glu Gln Gly 435 440 445
35	ACA TAC GCC CTG TCC CTC ATC TAT GGG AAG ACG GTG TAC CAC TAC CTC 1392 Thr Tyr Ala Leu Ser Leu Ile Tyr Gly Lys Thr Val Tyr His Tyr Leu 450 450
	ATC AGC CAA GAC AAG GCG GGC AAG TAC TGC ATT CCC GAG GGC ACC AAG 11e Ser Gln Asp Lys Ala Gly Lys Tyr Cys Ile Pro Glu Gly Thr Lys 470 475 480
40	TTT GAC ACG CTC TGG CAG CTG GTG GAG TAT CTG AAG CTG AAG GCG GAC Phe Asp Thr Leu Trp Gln Leu Val Glu Tyr Leu Lys Leu Lys Ala Asp 485 490 495
45	GGG CTC ATC TAC TGC CTG AAG GAG GCC TGC CCC AAC AGC AGT GCC AGC Gly Leu Ile Tyr Cys Leu Lys Glu Ala Cys Pro Asn Ser Ser Ala Ser 500 505 510
50	AAC GCC TCA GGG GCT GCT CCC ACA CTC CCA GCC CAC CCA TCC ACG Asn Ala Ser Gly Ala Ala Ala Pro Thr Leu Pro Ala His Pro Ser Thr 515 520 525
55	TTG ACT CAT CCT CAG AGA CGA ATC GAC ACC CTC AAC TCA GAT GGA TAC Leu Thr His Pro Gln Arg Arg Ile Asp Thr Leu Asn Ser Asp Gly Tyr 535 540
	ACC CCT GAG CCA GCA CGC ATA ACG TCC CCA GAC AAA CCG CGG CCG ATG 1680
	194

										195							
	Thr 545	Pro	Glu	Pro	Ala	Arg 550	Ile	Thr	Ser	Pro	Asp 555	Lys	Pro	Arg	Pro	Met 560	
5					AGC Ser 565												1728
10					AAG Lys												1776
15			_		GGC Gly										_		1824
15					AAG Lys												1872
20					AAG Lys												1920
25					CTG Leu 645												1968
30					GCC Ala												2016
25					TTC Phe												2064
35					CTG Leu												2112
40					TTT Phe												2160
45	_	_			CAC His 725		_										2208
50					GAC Asp												2256
55					TGG Trp												2304
00	TCC	AGC	CGC	AGC	GAT	GTC	TGG	AGC	TAT	GGG	GTC	ACC	ATG	TGG	GAG	GCC	2352

												190									
	S	Ser	Se 77	r A: 0	rg s	Ser	Asp	Val	Trp 775	Sei	ту:	r Gl	y Va	al T	hr 80	Met	Trp	G1	u.	Ala	
5	7	85		,		<i>3</i> ± <i>y</i>	OIII	790	CCC Pro	тух	гуy	з Ly	s Me	et L; 95	ys	Gly	Pro	G1	u '	Val 800	2400
10							805	GIII	GGC Gly	ьys	Arg	810	t G1	u C	ys	Pro	Pro	Gl:	u (5	Cys	2448
15					8	20	- y -	MIA	CTC Leu	мес	825	Asp	о Су	s Tı	сp	Ile	Tyr 830	Lys	3 T	rp	2496
	G <i>I</i> G]	AG lu	GAT Asp	CG Ar	J	CC (GAC Asp	TTC Phe	CTG Leu	ACC Thr 840	GTG Val	GAG Glu	G CA	G CC n Ar	g I	ATG Met 845	CGA Arg	GCC Ala	C T	'GT 'ys	2544
20	ТА Ту	C'r'	TAC Tyr 850	AG(C C	TG C	GCC . Ala	Der	AAG Lys 855	GTG Val	GAA Glu	GGG Gly	CCC Pro	C CC Pr 86	0 0	3GC 31y	AGC Ser	ACA Thr	G G	AG ln	2592
25	AA Ly 86	s A	GCT Ala	GA(G GC	CT G	la (TGT Cys 870	GCC Ala	TGA											2616
30			(i	.) s	EQU	ENC.	E CF	IARAC	FOR CTER:	ISTI	CS :	NO:	109:								
35				(B) (C) (D)	TY ST TO	PE: RANI POLO	ami DEDN DGY:	no a ESS: lin	sir sir ear	ngle											
40			(v) F	RAGI	MENT	ГТҮ	PE:	pro inte	rna	1										
,0	Met	· W							IPTI												
									lu L												
45									al A												
									hr T 4 ro V												
50									5 /s Pl												
									er A												
				le	Phe	Ph			sp As												
55									ır Le												

			115					120					125			
	Ile	Asp	Phe	Lys	Glu	Asp	Gly	Asn	Ile	Leu	Gly	His	Lys	Leu	Glu	Tyr
		130		-			135					140	-			-
	Asn	Tvr	Asn	Ser	His	Asn	Val	Tvr	Ile	Met	Ala	Asp	Lvs	Gln	Lvs	Asn
5	145	- 2 -				150					155				_,	160
•		тла	Lare	Val	λen		Luc	Tla	Ara	uic		716	G3.v	Asp	Gly	
	Gry	116	цуъ	vai	165	FIIC	шуз	116	Arg		ASII	116	Giu	Asp		Ser
		~ 7				· -		~ 1	01	170	-	_	-1-		175	a 1
	vai	GIn	Leu		Asp	HIS	Tyr	Gin		Asn	Thr	Pro	ше	Gly	Asp	GIY
				180					185					190		
10	Pro	Val	Leu	Leu	Pro	Asp	Asn	His	Tyr	Leu	Ser	Thr	Gln	Ser	Ala	Leu
			195					200					205			
	Ser	Lys	Asp	Pro	Asn	Glu	Lys	Arg	Asp	His	Met	Val	Leu	Leu	Glu	Phe
		210					215					220				
	Val	Thr	Ala	Ala	Gly	Ile	Thr	Leu	Gly	Met	Asp	Glu	Leu	Tyr	Lys	Ser
15	225					230					235					240
	Gly	Leu	Arq	Ser	Arq	Ala	Gln	Ala	Ser	Asn	Ser	Ala	Met	Pro	Asp	Pro
	-		_		245					250					255	
	Δla	Δla	His	Len	Pro	Phe	Phe	Tvr	Glv	_	Tle	Ser	Ara	Ala	Glu	Ala
				260				- 1 -	265				5	270		
20	Glu	Glu	Hic		Lvc	Len	λΊз	Gly		λΊэ	Aen	Gly	T.011	Phe	I.en	T.e.11
20	GIU	GIU		пса	цуз	Бец	AIG	280	PICC	ALG	пор	Gry	285	FIIC	шси	Бец
	7	61	275	7	3	0	T		G 3		*** 7	T		T	17-1	1114.
	Arg		Cys	Leu	Arg	ser		GIY	GTA	TAL	val		ser	Leu	val	HIS
		290					295	_				300				
	-	Val	Arg	Phe	His		Phe	Pro	lie	GLu	_	GIn	Leu	Asn	GIY	
25	305	_	_	_	_	310		_			315					320
	Tyr	Ala	Ile	Ala	-	Gly	Lys	Ala	His	-	Gly	Pro	Ala	Glu	Leu	Cys
					325					330					335	
	Glu	Phe	Tyr	Ser	Arg	Asp	Pro	Asp	Gly	Leu	Pro	Cys	Asn	Leu	Arg	Lys
				340					345					350		
30	Pro	Cys	Asn	Arg	Pro	Ser	Gly	Leu	Glu	Pro	Gln	Pro	Gly	Val	Phe	Asp
			355					360					365			
	Cys	Leu	Arq	Asp	Ala	Met	Val	Arq	Asp	Tyr	Val	Arq	Gln	Thr	Trp	Lys
	-	370	_	-			375	_	_	-		380				
	Leu	Glu	Glv	Glu	Ala	Leu	Glu	Gln	Ala	Ile	Ile	Ser	Gln	Ala	Pro	Gln
35	385		1			390					395					400
•		Glu	Lare	Len	Tle		Thr	Thr	λΊэ	Hie		Ara	Met	Pro	Trn	
	· · · ·	014	2,5	LCu	405				7114	410	Olu	mg			415	-1-
	1116	C ~ ~	Co~	T 011		7.~~	C1	C1	77-		A ~~~	T 1.00	1 011	Tyr		Clv
	nıs	Ser	261	420	1111	Arg	Giu	GIU		GIU	Arg	цуб	Leu	430	Ser	Gry
40		~1	m\		01. .	T .	Dk -	T	425		D		*		a 1-	~1
40	Ala	GIII		Asp	GIY	гÀг	Pne		reu	Arg	PIO	Arg	-	Glu	GIII	Gry
			435	_	_	_		440		_			445		_	_
	Thr	_	Ala	Leu	Ser	Leu		Tyr	GIA	Lys	Thr		Tyr	His	Tyr	Leu
		450					455					460				
	Ile	Ser	Gln	Asp	Lys	Ala	Gly	Lys	\mathtt{Tyr}	Cys	Ile	Pro	Glu	Gly	Thr	Lys
45	465					470					475					480
	Phe	Asp	Thr	Leu	Trp	Gln	Leu	Val	Glu	Tyr	Leu	Lys	Leu	Lys	Ala	Asp
					485					490					495	
	Gly	Leu	Ile	Tyr	Cys	Leu	Lys	Glu	Ala	Cys	Pro	Asn	Ser	Ser	Ala	Ser
				500					505	_				510		
50	Asn	Ala	Ser	Gly	Ala	Ala	Ala	Pro	Thr	Leu	Pro	Ala	His	Pro	Ser	Thr
			515					520			-		525			
	Lev	Thr		Pro	Gln	Ara	Ara		Asp	Thr	Lev	Asn		Asp	Glv	Tyr
		530					535		Р			540			1	-1-
	Thr		Glu	Pro	Ala	Ara		Thr	Ser	Pro	Asn		Pro	Ara	Pro	Met
55	545	110	O.L.U	0	u	550	110	****	SEL	FIO	555	Ly S	110	77.9		560
33		Mc+	7 ~~	Th ➤	Ser		Т1.~	۵1،۰	C.~~	D~~		E.~~	V c~	D~~	G1	Glu
	FIG	IJE L	Map	TII	JEI	val	TYL	GIU	Set	PIO	TAT	261	αsp	FΙŲ	Giu	GIU

198

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565
                                           570
        Leu Lys Asp Lys Lys Leu Phe Leu Lys Arg Asp Asn Leu Leu Ile Ala
                            585
        Asp Ile Glu Leu Gly Cys Gly Asn Phe Gly Ser Val Arg Gln Gly Val
   5
                                   600
        Tyr Arg Met Arg Lys Lys Gln Ile Asp Val Ala Ile Lys Val Leu Lys
                                                      605
                             615
        Gln Gly Thr Glu Lys Ala Asp Thr Glu Glu Met Met Arg Glu Ala Gln
                                                   620
                          630
                                               635
        Ile Met His Gln Leu Asp Asn Pro Tyr Ile Val Arg Leu Ile Gly Val
  10
                                          650
       Cys Gln Ala Glu Ala Leu Met Leu Val Met Glu Met Ala Gly Gly
                                    665
       Pro Leu His Lys Phe Leu Val Gly Lys Arg Glu Glu Ile Pro Val Ser
  15
                                 680
       Asn Val Ala Glu Leu Leu His Gln Val Ser Met Gly Met Lys Tyr Leu
                               695
       Glu Glu Lys Asn Phe Val His Arg Asp Leu Ala Ala Arg Asn Val Leu
                                                 700
                          710
       Leu Val Asn Arg His Tyr Ala Lys Ile Ser Asp Phe Gly Leu Ser Lys
                                             715
 20
                                 730
       Ala Leu Gly Ala Asp Asp Ser Tyr Tyr Thr Ala Arg Ser Ala Gly Lys
                   740
                                     745
       Trp Pro Leu Lys Trp Tyr Ala Pro Glu Cys Ile Asn Phe Arg Lys Phe
 25
                                  760
       Ser Ser Arg Ser Asp Val Trp Ser Tyr Gly Val Thr Met Trp Glu Ala
                            775
                                                  780
      Leu Ser Tyr Gly Gln Lys Pro Tyr Lys Lys Met Lys Gly Pro Glu Val
                         790
                                             795
      Met Ala Phe Ile Glu Gln Gly Lys Arg Met Glu Cys Pro Pro Glu Cys
 30
                                         810
      Pro Pro Glu Leu Tyr Ala Leu Met Ser Asp Cys Trp Ile Tyr Lys Trp
                  820
                                      825
      Glu Asp Arg Pro Asp Phe Leu Thr Val Glu Gln Arg Met Arg Ala Cys
 35
                                 840
                                                    845
      Tyr Tyr Ser Leu Ala Ser Lys Val Glu Gly Pro Pro Gly Ser Thr Gln
                           855
                                               860
      Lys Ala Glu Ala Ala Cys Ala
                         870
40
               (2) INFORMATION FOR SEQ ID NO:110:
            (i) SEQUENCE CHARACTERISTICS:
              (A) LENGTH: 2598 base pairs
45
              (B) TYPE: nucleic acid
              (C) STRANDEDNESS: single
              (D) TOPOLOGY: linear
            (ii) MOLECULE TYPE: cDNA
50
            (ix) FEATURE:
               (A) NAME/KEY: Coding Sequence
               (B) LOCATION: 1...2595
               (D) OTHER INFORMATION:
55
```

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:110:

. 199

				CCC Pro	_	_									_		48
5																	
	CGT	GCC	GAG	GCC	GAG	GAG	CAC	CTG	AAG	CTG	GCG	GGC	ATG	GCG	GAC	GGG	96
	Arg	Ala	Glu	Ala 20	Glu	Glu	His	Leu	Lys 25	Leu	Ala	Gly	Met	Ala 30	Asp	Gly	
10	CTC	TTC	CTG	CTG	CGC	CAG	TGC	CTG	CGC	TCG	CTG	GGC	GGC	TAT	GTG	CTG	144
	Leu	Phe	Leu 35	Leu	Arg	Gln	Cys	Leu 40	Arg	Ser	Leu	Gly	Gly 45	Tyr	Val	Leu	
	TCG	CTC	GTG	CAC	GAT	GTG	CGC	TTC	CAC	CAC	TTT	CCC	ATC	GAG	CGC	CAG	192
15	Ser	Leu 50	Val	His	Asp	Val	Arg 55	Phe	His	His	Phe	Pro 60	Ile	Glu	Arg	Gln	
	CTC	AAC	GGC	ACC	TAC	GCC	ATT	GCC	GGC	GGC	AAA	GCG	CAC	TGT	GGA	CCG	240
	Leu	Asn	Gly	Thr	Tyr	Ala	Ile	Ala	Gly	Gly	Lys	Ala	His	Cys	Gly	Pro	
20	65	ana	o ma	maa	an a	70	ma a	maa	000		75	an a	000	CTC	000	80 TCC	200
				TGC Cys													288
	niu	014	200	C , D	85	1110	- / -	501	9	90	110	пор	OI,	200	95	C/L	
25																	
				AAG											_		336
	Asn	Leu	Arg	Lys 100	Pro	Cys	Asn	Arg	Pro 105	Ser	Gly	Leu	Glu	Pro 110	Gln	Pro	
30	GGG	GTC	TTC	GAC	TGC	CTG	CGA	GAC	GCC	ATG	GTG	CGT	GAC	TAC	GTG	CGC	384
	Gly	Val	Phe 115	Asp	Cys	Leu	Arg	Asp 120	Ala	Met	Val	Arg	Asp 125	Tyr	Val	Arg	
	CAG	ACG	TGG	AAG	CTG	GAG	GGC	GAG	GCC	CTG	GAG	CAG	GCC	ATC	ATC	AGC	432
35	Gln	Thr 130	Trp	Lys	Leu	Glu	Gly 135	Glu	Ala	Leu	Glu	Gln 140	Ala	Ile	Ile	Ser	
	C A C	ccc	ccc	CAG	CTC	CNC	אאמ	CTTC	א מיינית	CCT	700	N.C.C	ccc	CAC	CAC	ccc	480
				Gln													400
40	145					150	-2-				155					160	
	ATG	CCC	TGG	TAC	CAC	AGC	AGC	CTG	ACG	CGT	GAG	GAG	GCC	GAG	CGC	AAA	528
4.5	Met	Pro	Trp	Tyr	His 165	Ser	Ser	Leu	Thr	Arg 170	Glu	Glu	Ala	Glu	Arg 175	Lys	
45	CODO	TAC	тст	GGG	ccc	CNC	7 CC	CNC	ccc	220	TTC	CTC	CTC	NGG	ccc	ccc	576
				Gly													376
	200	-7-	501	180		0111			185	272	11.0	Dou	200	190			
50				GGC													624
	Lys	Glu	Gln 195	Gly	Thr	Tyr	Ala	Leu 200	Ser	Leu	Ile	Tyr	Gly 205	Lys	Thr	Val	
	TAC	CAC	TAC	CTC	ATC	AGC	CAA	GAC	AAG	GCG	GGC	AAG	TAC	TGC	ATT	CCC	672
55	Tyr	His	Tyr	Leu	Ile	Ser	Gln	Asp	Lys	Ala	Gly	Lys	Tyr	Cys	Ile	Pro	
		210					215					220					

5	GAG GGC ACC AAG TTT GAC ACG CTC TGG CAG CTG GTG GAG TAT CTG AAG Glu Gly Thr Lys Phe Asp Thr Leu Trp Gln Leu Val Glu Tyr Leu Lys 235 CTG AAG GCG GAC GGG CTC ATC TAC TGC CTG AAG GAG GCC TGC CCC AAC Leu Lys Ala Asp Gly Leu Ile Tyr Cya Lys	720 768
10	245 250 255 AGC AGT GCC AGC AAC GCC TCA CCG GCT TCA CCG	700
	260 265 270	816
15	CAC CCA TCC ACG TTG ACT CAT CCT CAG AGA CGA ATC GAC ACC CTC AAC His Pro Ser Thr Leu Thr His Pro Gln Arg Arg Ile Asp Thr Leu Asn 275 280 285	864
20	TCA GAT GGA TAC ACC CCT GAG CCA GCA CGC ATA ACG TCC CCA GAC AAA Ser Asp Gly Tyr Thr Pro Glu Pro Ala Arg Ile Thr Ser Pro Asp Lys 290 295 300	912
25	CCG CGG CCG ATG CCC ATG GAC ACG AGC GTG TAT GAG AGC CCC TAC AGC Pro Arg Pro Met Pro Met Asp Thr Ser Val Tyr Glu Ser Pro Tyr Ser 310 315 320	960
	GAC CCA GAG GAG CTC AAG GAC AAG AAG CTC TTC CTG AAG CGC GAT AAC Asp Pro Glu Glu Leu Lys Asp Lys Leu Phe Leu Lys Arg Asp Asn 325 330 335	1008
30	CTC CTC ATA GCT GAC ATT GAA CTT GGC TGC GGC AAC TTT GGC TCA GTG Leu Leu Ile Ala Asp Ile Glu Leu Gly Cys Gly Asn Phe Gly Ser Val 340 345 350	1056
35	CGC CAG GGC GTG TAC CGC ATG CGC AAG AAG CAG ATC GAC GTG GCC ATC Arg Gln Gly Val Tyr Arg Met Arg Lys Lys Gln Ile Asp Val Ala Ile 355 360 365	1104
40	AAG GTG CTG AAG CAG GGC ACG GAG AAG GCA GAC ACG GAA GAG ATG ATG Lys Val Leu Lys Gln Gly Thr Glu Lys Ala Asp Thr Glu Glu Met Met 370 380	1152
45	CGC GAG GCG CAG ATC ATG CAC CAG CTG GAC AAC CCC TAC ATC GTG CGG Arg Glu Ala Gln Ile Met His Gln Leu Asp Asn Pro Tyr Ile Val Arg 390 395 400	1200
	CTC ATT GGC GTC TGC CAG GCC GAG GCC CTC ATG CTG GTC ATG GAG ATG Leu Ile Gly Val Cys Gln Ala Glu Ala Leu Met Leu Val Met Glu Met 405 410 415	1248
50	GCT GGG GGC GGG CCG CTG CAC AAG TTC CTG GTC GGC AAG AGG GAG GAG Ala Gly Gly Pro Leu His Lys Phe Leu Val Gly Lys Arg Glu Glu 420 425 430	1296
55	ATC CCT GTG AGC AAT GTG GCC GAG CTG CTG CAC CAG GTG TCC ATG GGG Ile Pro Val Ser Asn Val Ala Glu Leu Leu His Gln Val Ser Met Gly 435 440 445	1344
		200

5					GAG Glu							1392
					CTG Leu							1440
10					GCA Ala 485							1488
15		_	_		TGG Trp							1536
20					TCC Ser							1584
25			_	_	TTG Leu							1632
					ATG Met							1680
30			_		CCA Pro 565							1728
35					GAG Glu							1776
40			_		TAC Tyr							1824
45					AAG Lys							1872
					AGC Ser							1920
50	_				CTG Leu 645							1968
55		_	_		GAG Glu	_						2016

202

5	TTC ATC TGC ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val 675 680 685	2064
	ACC ACC CTG ACC TAC GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC Thr Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His 690 695 700	2112
10	ATG AAG CAG CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC Met Lys Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val 705 710 715 720	2160
15	CAG GAG CGC ACC ATC TTC TTC AAG GAC GGC AAC TAC AAG ACC CGC Gln Glu Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg 725 730 735	2208
20	GCC GAG GTG AAG TTC GAG GGC GAC ACC CTG GTG AAC CGC ATC GAG CTG Ala Glu Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu 740 745 750	2256
25	AAG GGC ATC GAC TTC AAG GAG GAC GGC AAC ATC CTG GGG CAC AAG CTG Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu 755 760 765	2304
	GAG TAC AAC TAC AAC AGC CAC AAC GTC TAT ATC ATG GCC GAC AAG CAG Glu Tyr Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln 770 780	2352
30	AAG AAC GGC ATC AAG GTG AAC TTC AAG ATC CGC CAC AAC ATC GAG GAC Lys Asn Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp 790 795 800	2400
35	GGC AGC GTG CAG CTC GCC GAC CAC TAC CAG CAG AAC ACC CCC ATC GGC Gly Ser Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly 805 810 815	2448
40	GAC GGC CCC GTG CTG CCC GAC AAC CAC TAC CTG AGC ACC CAG TCC Asp Gly Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser 820 825 830	2496
45	GCC CTG AGC AAA GAC CCC AAC GAG AAG CGC GAT CAC ATG GTC CTG CTG Ala Leu Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu 835	2544
	GAG TTC GTG ACC GCC GCC GGG ATC ACT CTC GGC ATG GAC GAG CTG TAC Glu Phe Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr 850 860	2592
50	AAG TAA Lys 865	2598

55 (2) INFORMATION FOR SEQ ID NO:111:

```
(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 865 amino acids(B) TYPE: amino acid
```

(C) STRANDEDNESS: single

5 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

10 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:111:

Met Pro Asp Pro Ala Ala His Leu Pro Phe Phe Tyr Gly Ser Ile Ser Arg Ala Glu Ala Glu Glu His Leu Lys Leu Ala Gly Met Ala Asp Gly Leu Phe Leu Leu Arg Gln Cys Leu Arg Ser Leu Gly Gly Tyr Val Leu Ser Leu Val His Asp Val Arg Phe His His Phe Pro Ile Glu Arg Gln Leu Asn Gly Thr Tyr Ala Ile Ala Gly Gly Lys Ala His Cys Gly Pro Ala Glu Leu Cys Glu Phe Tyr Ser Arg Asp Pro Asp Gly Leu Pro Cys Asn Leu Arg Lys Pro Cys Asn Arg Pro Ser Gly Leu Glu Pro Gln Pro Gly Val Phe Asp Cys Leu Arg Asp Ala Met Val Arg Asp Tyr Val Arg Gln Thr Trp Lys Leu Glu Gly Glu Ala Leu Glu Gln Ala Ile Ile Ser Gln Ala Pro Gln Val Glu Lys Leu Ile Ala Thr Thr Ala His Glu Arg Met Pro Trp Tyr His Ser Ser Leu Thr Arg Glu Glu Ala Glu Arg Lys Leu Tyr Ser Gly Ala Gln Thr Asp Gly Lys Phe Leu Leu Arg Pro Arg Lys Glu Gln Gly Thr Tyr Ala Leu Ser Leu Ile Tyr Gly Lys Thr Val Tyr His Tyr Leu Ile Ser Gln Asp Lys Ala Gly Lys Tyr Cys Ile Pro 210 215 Glu Gly Thr Lys Phe Asp Thr Leu Trp Gln Leu Val Glu Tyr Leu Lys Leu Lys Ala Asp Gly Leu Ile Tyr Cys Leu Lys Glu Ala Cys Pro Asn Ser Ser Ala Ser Asn Ala Ser Gly Ala Ala Ala Pro Thr Leu Pro Ala His Pro Ser Thr Leu Thr His Pro Gln Arg Arg Ile Asp Thr Leu Asn Ser Asp Gly Tyr Thr Pro Glu Pro Ala Arg Ile Thr Ser Pro Asp Lys Pro Arg Pro Met Pro Met Asp Thr Ser Val Tyr Glu Ser Pro Tyr Ser Asp Pro Glu Glu Leu Lys Asp Lys Lys Leu Phe Leu Lys Arg Asp Asn Leu Leu Ile Ala Asp Ile Glu Leu Gly Cys Gly Asn Phe Gly Ser Val Arg Gln Gly Val Tyr Arg Met Arg Lys Lys Gln Ile Asp Val Ala Ile

	204
	255
	Lys Val Leu Lys Gln Gly Thr Glu Lys Ala Asp Thr Glu Glu Met Met
	370 370 Arg Glu Ala Cla Tla Mai
5	Arg Glu Ala Gln Ile Met His Gln Leu Asp Asn Pro Tyr Ile Val Arg
	Let lie Gly Val Cys Gln Ala Glu Ala Leu Met Leu Val Met Glu Met
	Ala Gly Gly Pro Leu His Lys Phe Leu Val Gly Lys Arg Glu Glu
10	Ile Pro Val Ser Asn Val Ala Glu Leu Leu His Gln Val Ser Met Gly
	Met Lys Tyr Leu Glu Glu Lys Asn Phe Val His Arg Asp Leu Ala Ala 450 455
	4'50 455 460 Arg Asn Val Leu Leu Val Asn Arg Asn Val Leu Leu Val Asn Arg Asn Val Leu Leu Val Asn Arg Asn Val Asn Val Asn Arg Asn Val Asn Val Asn Arg Asn Val Asn Val Asn Val Asn Arg Asn Val A
15	Arg Asn Val Leu Leu Val Asn Arg His Tyr Ala Lys Ile Ser Asp Phe 465 470 475 480
	Gly Leu Ser Lys Ala Leu Gly Ala Asp Asp Ser Tyr Tyr Thr Ala Arg 485 490
	Ser Ala Gly Lys Trp Pro Leu Lys Trp Tyr Ala Pro Glu Cys Ile Asn
20	Phe Arg Lys Phe Ser Ser Arg Ser Asp Val Trp Ser Tyr Gly Val Thr 515 520
	Met Trp Glu Ala Leu Ser Tyr Gly Gln Lys Pro Tyr Lys Lys Met Lys
25	Gly Pro Glu Val Met Ala Phe Ile Glu Gln Gly Lys Arg Met Glu Cys
25	545 550 555 560
	Pro Pro Glu Cys Pro Pro Glu Leu Tyr Ala Leu Met Ser Asp Cys Trp 565 570
	The Tyr Lys Trp Glu Asp Arg Pro Asp Phe Leu Thr Val Glu Gln Arg
30	Met Arg Ala Cys Tyr Tyr Ser Leu Ala Ser Lys Val Glu Gly Pro Pro
	Gly Ser Thr Gln Lys Ala Glu Ala Ala Cys Ala Trp Asp Pro Pro Val
	Ala Thr Met Val Ser Lyo Character 620
35	Ala Thr Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro 625 630 635
	11e Leu Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val
	Ser Gly Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys
40	Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val
	Thr Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His
	690 695 700 Met Lys Gln His Asp Phe Phe Lys G
45	Met Lys Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val 705 710 715 720
	Gln Glu Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg 725 730 737
	740 The Leu Val Asn Arg Ile Glu Leu
50	Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu
	Glu Tyr Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln
55	Lys Asn Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp
55	785 790 795 800
	Gly Ser Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly

	Asp	Gly	Pro	Val 820	805 Leu	Leu	Pro	Asp	Asn 825	810 His	Tyr	Leu	Ser	Thr 830	815 Gln	Ser	
5	Ala	Leu	Ser 835		Asp	Pro	Asn	Glu 840		Arg	Asp	His	Met 845	Val	Leu	Leu	
		Phe 850		Thr	Ala	Ala	Gly 855		Thr	Leu	Gly	Met 860		Glu	Leu	Tyr	
10	Lуs 865																
			(2)	INI	FORM	ATIO1	1 FOF	SE(O ID	NO:	112:						
15		()	(A) (B) (C)	EQUEN LENC TYPE STRA TOPO	ETH: E: nu ANDEI	1639 uclei ONESS	bas ic ac S: si	se pa cid ingle	airs								
20				OLEC		TYPI	E: CI	ONA									
25			(B)	NAM LOC OTI	CATIO	ON:	l	1632	equer	nce							
23		()	ki) S	SEQUE	ENCE	DESC	CRIPT	rion	: SE(Q ID	NO:	112:					
30														ACG Thr		_	48
25														GTG Val 30			96
35														AGT Ser			144
40														AAT Asn			192
45														CTG Leu			240
50														TCT Ser			288
EE														CAG Gln 110			336
55	CAG	GGC	CTA	GCT	TTC	TGC	CAT	TCT	CAT	CGG	GTC	CTC	CAC	CGA	GAC	CTT	384 . 205

										20									
	Gl	n G	ly L. 1	eu A. 15	la Pl	ne Cy	s Hi	is Se 12	er Hi 20	is A	rg V	al L		is . 25	Arg	J As	p Leu		
5	AA Ly		CT C ro G 30	AG AA ln As	AT CT	rg CI eu Le	T AT u Il	e As	AC AC	A GA	AG G	ly A	CC A la I 40	TC I	AAG Lys	CT Le	A GCA u Ala	4	32
10	GA As 14		TT GO	GA CI Ly Le	TA GC	C AG a Ar 15	y AI	T TT a Ph	T GG e Gl	A GI y Va	CC CC	co Va	TT C	GT 1 rg 1	ACT Thr	TA:	C ACC r Thr 160	4	80
15	CA' Hi:	T GA s Gl	G GI u Va	TG GT	G AC 1 Th 16	т пе	G TG u Tr	G TA p Ty	C CG	A GC g Al 17	a Pi	T GA	AA A' lu I	TC (CTC Leu	CTC Let	G GGC u Gly	5:	28
		,	1	18	0	1 111.	r AT	a va.	1 As ₁	0 Il 5	e Tr	p Se	er Le	eu G 1	1y 90	Cys	C ATC	51	76
20	TT7 Phe	GC Al	T GA a Gl		G GTO	G ACT	CG(C CGC G Arg 200	3 AT	C CTO	G TT u Ph	C CC e Pr	T GO O Gl 20	уА	AT sp	TCT Ser	GAG Glu	62	24
25	ATT	GAG Asp 210		G CTO	TTC Phe	C CGG Arg	11e 215	: Pne	CGG Arg	AC'	r Cr	G GG u G1 22	y Th	C C	CA ro	GAT Asp	GAG Glu	67	2
30	GTG Val 225		TGC Trp	G CCA	A GGA O Gly	GTT Val 230	1111	TCT Ser	ATG Met	Pro	GA' As ₁	Ty:	C AA r Ly	G Co	CA co	AGT Ser	TTC Phe 240	72	0
35	CCC Pro	AAC Lys	TGG Trp	GCC Ala	CGG Arg 245	CAA Gln	GAT Asp	TTT Phe	'AGT Ser	AAA Lys 250	Va]	GT/	A CC	r co	: o	CTG Leu 255	GAT Asp	76	8
	GAA Glu	GAT Asp	GGA Gly	CGG Arg 260	Der	TTG Leu	TTA Leu	TCG Ser	CAA Gln 265	ATG Met	Leu	CAC His	С ТАС 5 Туз	C GA As	p l	CCT Pro	AAC Asn	816	5
40	AAG Lys	CGG Arg	ATT Ile 275		GCC Ala	AAG Lys	GCA Ala	GCC Ala 280	CTG Leu	GCT Ala	CAC His	CCT Pro	TTC Phe 285	Ph	с (.e (CAG Gln	GAT Asp	864	ı
45	GTG Val	ACC Thr 290	AAG Lys	CCA Pro	GTA Val	CCC Pro	CAT His 295	CTT Leu	CGA Arg	CTC Leu	TGG Trp	GAT Asp 300	Pro	CC Pr	G G O V	STC /al	GCC Ala	912	!
50	ACC Thr 305	ATG Met	GTG Val	AGC Ser	AAG Lys	GGC Gly 310	GAG Glu	GAG Glu	CTG Leu	TTC Phe	ACC Thr 315	GGG Gly	GTG Val	GT(G C	ro	ATC Ile 320	960	
55	CTG Leu	GTC Val	GAG Glu	CTG Leu	GAC Asp 325	GGC Gly	GAC Asp	GTA Val	Asn	GGC Gly 330	CAC His	AAG Lys	TTC Phe	AG(Se)	r V	TG al a	TCC Ser	1008	
	GGC (GAG	GGC	GAG	GGC	GAT	GCC .	ACC	TAC	GGC	AAG	CTG	ACC	CTO	€ A.	AG :	FTC	1056	206

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										207								
	Gly	Glu	Gly	Glu 340	Gly	Asp	Ala	Thr	Tyr 345	Gly	Lys	Leu	Thr	Leu 350	Lys	Phe		
5												CCC Pro						1104
10												TAC Tyr 380						1152
15												GAA Glu			_	_		1200
10												TAC Tyr		_				1248
20												CGC Arg						1296
25												GGG Gly						1344
30												GCC Ala 460						1392
35												AAC Asn						1440
33												ACC Thr						1488
40												AGC Ser						1536
45												ATG Met						1584
50												GAC Asp 540				AAG Lys	Т	1633
	AA																	1635

(2) INFORMATION FOR SEQ ID NO:113:

(i) SEQUENCE CHARACTERISTICS:

```
(A) LENGTH: 544 amino acids
(B) TYPE: amino acid
```

- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:113:

Met Glu Asn Phe Gln Lys Val Glu Lys Ile Gly Glu Gly Thr Tyr Gly Val Val Tyr Lys Ala Arg Asn Lys Leu Thr Gly Glu Val Val Ala Leu Lys Lys Ile Arg Leu Asp Thr Glu Thr Glu Gly Val Pro Ser Thr Ala Ile Arg Glu Ile Ser Leu Leu Lys Glu Leu Asn His Pro Asn Ile Val Lys Leu Leu Asp Val Ile His Thr Glu Asn Lys Leu Tyr Leu Val Phe Glu Phe Leu His Gln Asp Leu Lys Lys Phe Met Asp Ala Ser Ala Leu Thr Gly Ile Pro Leu Pro Leu Ile Lys Ser Tyr Leu Phe Gln Leu Leu Gln Gly Leu Ala Phe Cys His Ser His Arg Val Leu His Arg Asp Leu Lys Pro Gln Asn Leu Leu Ile Asn Thr Glu Gly Ala Ile Lys Leu Ala Asp Phe Gly Leu Ala Arg Ala Phe Gly Val Pro Val Arg Thr Tyr Thr His Glu Val Val Thr Leu Trp Tyr Arg Ala Pro Glu Ile Leu Leu Gly Ser Lys Tyr Tyr Ser Thr Ala Val Asp Ile Trp Ser Leu Gly Cys Ile Phe Ala Glu Met Val Thr Arg Arg Ala Leu Phe Pro Gly Asp Ser Glu Ile Asp Gln Leu Phe Arg Ile Phe Arg Thr Leu Gly Thr Pro Asp Glu Val Val Trp Pro Gly Val Thr Ser Met Pro Asp Tyr Lys Pro Ser Phe Pro Lys Trp Ala Arg Gln Asp Phe Ser Lys Val Val Pro Pro Leu Asp Glu Asp Gly Arg Ser Leu Leu Ser Gln Met Leu His Tyr Asp Pro Asn Lys Arg Ile Ser Ala Lys Ala Ala Leu Ala His Pro Phe Phe Gln Asp Val Thr Lys Pro Val Pro His Leu Arg Leu Trp Asp Pro Pro Val Ala Thr Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr

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										200							
	Thr	Leu 370	Thr	Tyr	Gly	Val	Gln 375	Cys	Phe	Ser	Arg	Tyr 380	Pro	Asp	His	Met	
	Lys 385	_	His	Asp	Phe	Phe 390		Ser	Ala	Met	Pro 395		Gly	Tyr	Val	Gln 400	
5		Arg	Thr	Ile	Phe		Lys	Asp	Asp	_		Tyr	Lys	Thr	_		
	Glu	Val	Lys		405 Glu	Gly	Asp	Thr		410 Val	Asn	Arg	Ile		415 Leu	Lys	
	Glv	Tle	Asn	420 Phe	Lys	Glu	Δsn	Glv	425 Agn	Tle	I.eu	Glv	Hic	430	Len	Glu	
10	dry		435	1110	2,0	Olu	пор	440	Abii	110	Deu	Cly	445	2,5	Deu	Ozu	
	Tyr	Asn 450	Tyr	Asn	Ser	His	Asn 455	Val	Tyr	Ile	Met	Ala 460	Asp	Lys	Gln	Lys	
	Asn 465	Gly	Ile	Lys	Val	Asn 470	Phe	Lys	Ile	Arg	His 475	Asn	Ile	Glu	Asp	Gly 480	
15		Val	Gln	Leu	Ala		His	Tyr	Gln	Gln		Thr	Pro	Ile	Gly		
	Glv	Pro	Val	Leu	485 Leu	Pro	Asp	Asn	His	490 Tvr	Leu	Ser	Thr	Gln	495 Ser	Ala	
	,			500					505	-1-				510			
20	Leu	Ser	Lys 515	Asp	Pro	Asn	Glu	Lys 520	Arg	Asp	His	Met	Val 525	Leu	Leu	Glu	
	Phe		Thr	Ala	Ala	Gly		Thr	Leu	Gly	Met			Leu	Tyr	Lys	
		530					535					540					
05			(2)	INI	FORMA	OITA	1 FOI	SE(QI Q	ио::	114:						
25		(1	i) sī	EOUEI	NCE (HARZ	CTE	ereri	rcs ·								
		(-		-	GTH:												
					E: nւ												
30					ANDEI OLOGY			-	2								
		, :		401 E		mwn.	7 . mT										
				FEAT	CULE JRE:	IIF	3. CI	JNA									
35			(A)	ו או	ME/KE	ε γ · (odir	nor Se	omer	nce.							
00					CATIO			_	-quei	100							
			(D)	OTI	HER]	INFO	RMAT	ON:									
40		(2	ci) S	EQUI	ENCE	DESC	CRIPT	rion	SE(QI Ç	NO:	114:					
40	ATG	GTG	AGC	AAG	GGC	GAG	GAG	CTG	TTC	ACC	GGG	GTG	GTG	CCC	ATC	CTG	48
	Met				Gly					Thr					Ile		
	1				5					10					15		
45					GGC												96
	Val	Glu	Leu	Asp 20	Gly	Asp	Val	Asn	Gly 25	His	Lys	Phe	Ser	Val 30	Ser	Gly	
50					GAT Asp												144
-	JIU	31 y	35	Эху	vab	A1G	1111	40	GIY	מענ	nea	1111	45	шys	FIIC	110	
	TGC	ACC	ACC	GGC	AAG	CTG	CCC	GTG	CCC	TGG	ccc	ACC	CTC	GTG	ACC	ACC	192
55		Thr			Lys		Pro					Thr					
55		50					55					60					

	65	•			-, ,	7	0	у 5 Р.	ne s	er 1	Arg	Tyr 75	Pro	o As	рн	is.	Met	G AAG Lys 80	240
5	CA Gl	G C. n H.	AC G is A	AC T	TC T he Pl 8!		AG To ys Se	CC G(er Al	CC A la M	et 1	ccc Pro	GAA Glu	GG(Gl _}	TA Ty:	C Gʻ r Va	al (CAG Gln 95	GAG Glu	288
10	CG Ar	C AG	CC A		rc Ti ne Pl	rc Al	AG GA Ys As	AC GA	sp G	GC A ly A 05	AC	TAC Tyr	AAG Lys	ACC Thi	C CC r Ai	g	SCC Ala	GAG Glu	336
15	GT(Va)	G AA l Ly	AG TT 's Pl 11	rc ga ne gl	AG GO .u Gl	C GA Y As	AC AC	C CI r Le 12	u va	rg a al A	AC sn	CGC Arg	ATC Ile	GAC Glu 125	ı Le	G A	·γs	GGC Gly	384
20	ATC Ile	C GA ≥ As 13	C TI p Ph 0	C AA e Ly	G GA	G GA u As	C GG P G1 13	y As	C Al	CC C	TG (GGG Gly	CAC His 140	AAG Lys	CT Le	G G u G	AG lu	TAC Tyr	432
	AAC Asn 145	TA Ty	C AA r As	C AG n Se	C CA r Hi	C AA s As 15	ıı va	C TA	T AT	C A	et A	GCC Ala 155	GAC Asp	AAG Lys	CA Gl	G A	AG ys	AAC Asn 160	480
25	GGC Gly	ATC	C AA	G GT	G AAG l Ası 165	T E110	C AAG e Lys	G ATO	CG Ar	C C# g Hi 17	s A	AAC . Asn	ATC Ile	GAG Glu	GA:	G.	GC ly 75	AGC Ser	528
30	GTG Val	CA(CTO	C GC0 1 Ala 180	C GAO A Asp	CAC His	TAC Tyr	CAC Glr	G CA(1 Gl) 18!	n As	C A	CC (CCC Pro	ATC Ile	GG(Gl _y 190	' As	AC sp	GGC Gly	576
35	CCC Pro	GTC Val	CTC Leu 195		CCC Pro	GAC Asp	AAC Asn	CAC His	Ty	C CT	G A u S	GC A	Thr	CAG Gln 205	TCC Ser	GC Al	:C (CTG Leu	624
40	AGC Ser	AAA Lys 210	GAC Asp	CCC Pro	AAC Asn	GAG Glu	AAG Lys 215	CGC Arg	GAT Asp	CA Hi	C A'	et V	TC (al 1	CTG Leu	CTG Leu	GA Gl	G 7	ITC Phe	672
	GTG Val 225	ACC Thr	GCC Ala	GCC Ala	GGG Gly	ATC Ile 230	ACT Thr	CTC Leu	GGC	AT(G G/ C As 23	sp G	AG (CTG Leu	TAC Tyr	AA Ly	s S	CCC Ser 240	720
45	GGA Gly	CTC Leu	AGA Arg	TCT Ser	CGA Arg 245	GCC Ala	ATG Met	GAG Glu	AAC Asn	TTC Phe 250	e G1	AA A	AG (STG (GAA Glu	AA(Ly:	3 I	TC le	768
50	GGA (GAG Glu	GGC Gly	ACG Thr 260	TAC Tyr	GGA Gly	GTT Val	GTG Val	TAC Tyr 265	AAA Lys	GC Al	C A	GA A rg A	sn I	AAG Lys 270	TT(Let	A I T	.CG hr	816
55	GGA (GAG Glu	GTG Val 275	GTG Val	GCG Ala	CTT Leu	ъда	AAA Lys 280	ATC Ile	CGC Arg	CT Le	G GA	T q	CT (hr (GAG Glu	ACT Thr	G G	AG lu	864

						211					
			ACT Thr								912
5			ATT Ile								960
10			GTT Val 325								1008
15			GCT Ala								1056
			CTG Leu								1104
20			GAC Asp					_	_		1152
25			CTA Leu								1200
30			TAC Tyr 405								1248
35			CTG Leu							_	1296
40			TGC Cys						_		1344
70			TCT Ser								1392
45			GAT Asp								1440
50			AGT Ser 485								1488
55			CTG Leu						_		1536

	212	
	CTG CAC TAC GAC CCT AAC AAG CGG ATT TCG GCC AAG GCA GCC CTG GCT Leu His Tyr Asp Pro Asn Lys Arg Ile Ser Ala Lys Ala Ala Leu Ala 515 520 525	1584
5	CAC CCT TTC TTC CAG GAT GTG ACC AAG CCA GTA CCC CAT CTT CGA CTC T His Pro Phe Phe Gln Asp Val Thr Lys Pro Val Pro His Leu Arg Leu 530 535 540	1633
10	GA (C) TYPERING	1635
	(2) INFORMATION FOR SEQ ID NO:115:	
15	 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 544 amino acids (B) TYPE: amino acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 	
20	<pre>(ii) MOLECULE TYPE: protein (v) FRAGMENT TYPE: internal</pre>	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:115:	
25	Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu	
20		
	Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 20 25	
	Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile	
30	4U	
	Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr	
	Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp Hig Mot Lu-	
35	Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu 85 90	
	Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu	
	Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly 115 120 125	
40	Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr	
	Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn 145 150	
45	Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser	
45		
	Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly 180 185	
	Pro Val Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu	
50		
	Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe	
	Val Thr Ala Ala Gly Ile Thr Leu Gly Met Acr Cly You The	
55	Gly Leu Arg Ser Arg Ala Met Glu Asn Phe Gln Lys Val Glu Lys Ile	
	Gly Glu Gly Thr Tyr Gly Val Val Tyr Lys Ala Arg Asn Lys Leu Thr	

PCT/DK98/00145 WO 98/45704

213

										213							
				260					265					270			
	Gly	Glu	Val 275	Val	Ala	Leu	Lys	Lys 280	Ile	Arg	Leu	Asp	Thr 285	Glu	Thr	Glu	
5	Gly	Val 290	Pro	Ser	Thr	Ala	Ile 295	Arg	Glu	Ile	Ser	Leu 300	Leu	Lys	Glu	Leu	
	Asn 305	His	Pro	Asn	Ile	Val 310	Lys	Leu	Leu	Asp	Val 315	Ile	His	Thr	Glu	Asn 320	
		Leu	Tyr	Leu	Val 325		Glu	Phe	Leu	His 330		Asp	Leu	Lys	Lys 335		
10	Met	Asp	Ala	Ser 340	Ala	Leu	Thr	Gly	Ile 345		Leu	Pro	Leu	Ile 350		Ser	
	Tyr	Leu	Phe		Leu	Leu	Gln	Gly 360	-	Ala	Phe	Cys	His 365		His	Arg	
	Val	Leu		Arg	Asp	Leu	Lvs		Gln	Asn	Leu	Leu		Asn	Thr	Glu	
15		370			•		375					380					
	Gly 385	Ala	Ile	Lys	Leu	Ala 390	Asp	Phe	Gly	Leu	Ala 395	Arg	Ala	Phe	Gly	Val 400	
	Pro	Val	Arg	Thr	Tyr 405	Thr	His	Glu	Val	Val 410	Thr	Leu	Trp	Туr	Arg 415	Ala	
20	Pro	Glu	Ile	Leu 420	Leu	Gly	Ser	Lys	Tyr 425	Tyr	Ser	Thr	Ala	Val 430	Asp	Ile	
	Trp	Ser	Leu 435	Gly	Суѕ	Ile	Phe	Ala 440	Glu	Met	Val	Thr	Arg 445	Arg	Ala	Leu	
25	Phe	Pro 450	Gly	Asp	Ser	Glu	Ile 455	Asp	Gln	Leu	Phe	Arg 460	Ile	Phe	Arg	Thr	
		Gly	Thr	Pro	Asp		Val	Val	Trp	Pro	_	Val	Thr	Ser	Met		
	465	T1~	Tue	Dro	Sor	470	D×o	T 1/0	T~n	חות	475	<i>a</i> 15	7 an	Dho	ee*	480 Lvc	
00	_	-	-		Ser 485			_	_	490	_		_		495	_	
30				500	Leu	_		_	505	_				510			
			515	-	Pro		_	520				_	525				
35	His	Pro 530	Phe	Phe	Gln	Asp	Val 535	Thr	Lys	Pro	Val	Pro 540	His	Leu	Arg	Leu	
			(2)	INI	FORM	ATIO	1 FOI	R SE	Q ID	NO:	116:						
		(:	i) SI	EQUE	NCE (CHARA	ACTE	RIST	ics:								
40			(A)	LEN	GTH:	2532	2 bas	se pa	airs								
					E: n												
					ANDE! OLOG			_	9								
45		(:	ii) M	MOLE	CULE	TYPI	E: cl	ONA									
		(:	ix) 1	FEAT	URE:												
			(A)	NAI	ME/K	EY: (Codi	ng S	eque	nce							
50					CATION TO THE REPORT TO THE RE												
		(3			ENCE				: SE	Q ID	NO:	116:					
				-						-							
55					GGC Gly												48
	1			. 1-	5					10	1				15		
																	•

5					20	Oly	ASI	y va	I AS	sn (31y 25	Hi	s Ly	rs P	he	Ser	7 Va 30	l S	er	GGC Gly	96
	GA: Gl:	G G(4 -	AG lu 5	GGC Gly	GAT Asp	GCC Ala	C AC	C TA r Ty 40	T	GC Sly	AA(G CT	G A	CC hr	CTG Leu 45	AA Ly	G T	rc 1e	ATC Ile	144
10	TG(Cys	C AC S Th	-	CC (GGC Gly	AAG Lys	CTO	CC Pro	C GT D Va	G C	cc ro	TGC Trp	G CC	C A(O Th	hr	CTC Leu	GT(G AC	cc	ACC Thr	192
15	CTC Lev 65	AC Th	C T	AC (yr (GGC Gly	GTG Val	CAG Gln 70	TGC	C TT	C A e S	GC er	CGC Arg	TAC Ty:	C CC r Pr	CC (GAC Asp	CAC	C AT	G	AAG Lys 80	240
20			-	· P ·		85	пуъ	ser	GCC Ala	a M	et	Pro 90	Gli	ı Gl	у 1	Гуr	Val	. G1 95	n	Glu	288
25	- 3			1	00	rne	цуѕ	Asp	GAC Asp	1 (1y . 05	Asn	Tyr	. Ly	s 1	Phr	Arg 110	Ala	a. (Glu	336
			11	5		Oly	Asp	1111	CTG Leu 120	l Va	II A	Asn	Arg	Ile	e G 1	:lu :25	Leu	Ьys	3 (Gly	384
30	ATC Ile	GAC Asp 130		CA eL	AG (GAG Glu	GAC Asp	GGC Gly 135	AAC Asn	AT Il	C (CTG Leu	GGG Gly	CAC His	s L	AG ys	CTG Leu	GAC Glu	; 7	ΓAC Γyr	432
35	AAC Asn 145	TAC	AA Ası	C AC	GC C	113, 4	AAC Asn 150	GTC Val	TAT Tyr	AT Il	C A	ATG Met	GCC Ala 155	GAC Asp	C A	AG (CAG Gln	AAG Lys	A	AAC Asn .60	480
40	GGC	ATC Ile	AA(Lys	G GT S Va	. T	AC : sn 1 65	FTC .	AAG Lys	ATC Ile	CG Ar	gн	AC is	AAC Asn	ATC	GZ GZ	AG (lu <i>l</i>	GAC Asp	GGC Gly 175	A S	GC Ser	528
45	GTG Val	CAG Gln	CTC	GC Al 18	a A	AC C	CAC '	TAC Tyr	CAG Gln	CA(Gl: 185	n A	AC /	ACC Thr	CCC Pro	' A'I	le G	GC Hy	GAC Asp	G	GC 1y	576
	CCC (GTG Val	CTG Leu 195		G C	CC G	ac /	ısn	CAC His 200	ТАС Туз	C C	TG A	AGC Ser	ACC Thr	CA G1 20	n s	CC er	GCC Ala	C'	TG eu	624
50	AGC I	AAA Lys 210	GAC Asp	CC Pr	C AA	AC G	+u 1	AG ys 1	CGC Arg	GAT Asp	C CI	AC A	1et	GTC Val 220	CT Le	G C	TG (GAG Glu	T?	rc he	672
55	GTG A Val 7 225	ACC Thr	GCC Ala	GC(C GC	-у т	TC A le T 30	CT (CTC Leu	GGC Gly	: AT	et A	SAC (GAG Glu	CT	GT.	AC 1	AAG Lys	T(Se 24	er	720

	_		CGA Arg 245	_						768
5			GAT Asp							816
10			GCT Ala							864
15		_	GTG Val	_						912
20			TAT Tyr							960
25			GAG Glu 325					 		1008
			ATC Ile							1056
30			AGG Arg							1104
35			CAG Gln							1152
40			CAG Gln							1200
45			GGC Gly 405							1248
			GGT Gly							1296
50			GAC Asp							1344
55			GCC Ala							1392

5	465					116	Giu	ASI	Arg	475	. Leu	Glu	. Leu	Asn	Lys 480	1440
	AAG C	:AG G	AG TC lu Se	C GAG F Gli 48!	~p	ACA Thr	GCC Ala	AAG Lys	GCT Ala 490	Gly	TTC Phe	TGG Trp	GAG Glu	GAG Glu 495	TTT Phe	1488
10	GAG A Glu S	GT T	TG CA eu Gl 50		G CAG	GAG Glu	GTG Val	AAG Lys 505	AAC Asn	TTG Leu	CAC His	CAG Gln	CGT Arg 510	CTG Leu	GAA Glu	1536
15	GGG C	51	.5		11511	цув	520	гÀ2	Asn	Arg	Tyr	Lys 525	Asn	Ile	Leu	1584
20	CCC Tr	30			9	535	rre	тел	GIn	Gly	Arg 540	Asp	Ser	Asn	Ile	1632
25	CCC GC Pro Gl 545	_		-1-	550	1511 }	ııa.	ASN	Tyr	11e 555	Lys .	Asn	Gln	Leu	Leu 560	1680
	GGC CC	•		565	711U 1	ays 1	III .	ıyr	11e . 570	Ala	Ser (Gln (Gly	Cys : 575	Leu	1728
30	GAG GC Glu Al	C AC(a Thi	GTC Val 580	AAT Asn	GAC 1 Asp F	TC T	rp (CAG : Sln : 885	ATG (Met <i>l</i>	GCG '	TGG (3ln (GAG A Glu A	AAC A Asn S	AGC Ser	1776
35	CGT GTO Arg Val	C ATO l Ile 595	GTC Val	ATG Met	ACC A Thr T	III M.	GA G rg G	SAG (GTG (GAG A	ys G	GC C ly A	GG A	AAC A Asn I	AAA Yas	1824
40	TGC GTC Cys Val 610)	•	-	6	15	31 G	тум	let G	iln A	rg A 20	la T	yr G	ly P	ro	1872
45	TAC TCT Tyr Ser 625			(30	ry Gi	u H	1S A	sp T 6	hr T 35	hr G	lu T	yr L	ys F	eu 40	1920
50	CGT ACC			645		.о де	u As	5p A	sn G. 50	ly A	sp Le	eu I	le A:	rg G: 55	lu	1968
50	ATC TGG Ile Trp		660)	u se	66	55	co As	sp H:	is Gl	y Va 67	al Pi 70	co Se	er	2016
55	GAG CCT Glu Pro	GGG Gly 675	GGT (GTC C Val L	TC AG eu Se	C TTO r Pho 680	a re	G GA u As	AC CA	AG AT	CC AA Le As 68	n Gl	G CC n Ar	G CA	AG .n	2064

5		AGT Ser 690															2112
3	_	GGC Gly													_		2160
10		TCC Ser															2208
15		ATG Met							_					_	_		2256
20		AAG Lys															2304
0.5		AAG Lys 770													_		2352
25		AAC Asn															2400
30		CGC Arg															2448
35		AAG Lys													_		2496
40		GAG Glu										TGA					2532
45		1			FORM					NO:	117:						٠
45		(.	(A) (B) (C)	LENG TYP:	GTH: E: an ANDE	843 mino DNES	ami aci S: s	no a d ingl	cids								
50			ii)	MOLE	CULE	TYP	E: p	rote									
55					ENCE												
	Met	Val	Ser	Lys	Gly	Glu	Glu	Leu	Phe	Thr	Gly	Val	Val	Pro	Ile	Leu	3.

												218	3						
		1				5						10)					15	
												у Ні	s Ly				al .	Ser	Gly
5	G]	lu G	ly o	31u 55	Gly	/ As	p Al	ат	hr	Tyr	Gly	у Lу	s Le	eu Th		u L	ys 1	Phe	lle
	СУ	/s T 5	hr 1 0	hr	Gly	/ Ly	s Le	u P:	ro	Val	Pro	o Tr	p Pı	o Th	r Le	u V	al :	Thr	Thr
	Le 65	u T	hr 1	'yr	Gly	⁄ Va	l G1 70	n C	ys	Phe	Ser	r Ar	g Ty	60 r Pr	o As	р Н	is M	1et	Lys
10	Gl	n H	is A	.sp	Phe	Ph 85			er.	Ala	Met	: Pr	75 0 Gl	u Gl	у Ту	r Va	al C	Sln	80 Glu
	Ar	g T	hr I	le	Phe	Ph	е Lу	s As	gp.	Asp	Gly	90 As:	п Ту	r Ly	s Th	r Ai	g P	95 Ala	Glu
15			ys P						ır :	Leu	105								Gly
	11	e As			Lys	Glı	ı As	p G1	у	120 Asn	Ile	Le	u Gl	у Ні	12 s Ly	5 s Le	eu G	lu	Tyr
								n Va					al Al	14 a As					
20	Gl	y Il	le L	ys	Val	Asr	ı Phe	e Ly	s :	Ile	Arg	His	15 : As:	n Ile	e Gli	u As	മദ	lν	160 Ser
							,					177	1	r Pro			_		
or														Thi					
25																			
														220					
30														220 Glu					
						473						つにん		Trp					
				•	~ ~ ~						265			Gly					
35				_						ชบ				Gln	205				
			•					29:	3					Ile 300					
40														Lys					
40														Gly				n A	Asp
														Leu			Se	r /	
45														Ser		Gly	Gl		
								3/3						Thr	Phe				
	Glu 385	Ser	Lei	1 5	er (Gln	Pro 390	Gly	As	ı qa	he '	Val	Leu	Ser	Val	Leu	Se	r A	Asp
50		Pro	Lys	A	la (31y 105		Gly	Se	er F	ro I	Leu	395 Arg	Val	Thr	His	11	4 e L	ys •ys
	Val	Met	Сув	G 4	lu (Sly	Gly	Arg	ту	r I	hr '	410 Val	Gly	Gly	Leu	Glu	41: Th:	5 rP	he
55	Asp	Ser	Leu 435	T		Asp	Leu	Val	G1 44	u H	25 lis 1	Phe	Lys	Lys		430 Gly	Ile	e G	lu
	Glu	Ala			ly A	la	Phe	Val	Ту	r L	eu A	Arg	Gln	Pro	445 Tyr	Tyr	Ala	а Т	hr

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450
                          455
                                            460
     Arg Val Asn Ala Ala Asp Ile Glu Asn Arg Val Leu Glu Leu Asn Lys
             470
                             475
     Lys Gln Glu Ser Glu Asp Thr Ala Lys Ala Gly Phe Trp Glu Glu Phe
5
                                    490
                  485
     Glu Ser Leu Gln Lys Gln Glu Val Lys Asn Leu His Gln Arg Leu Glu
              500
                                 505
                                                  510
     Gly Gln Arg Pro Glu Asn Lys Gly Lys Asn Arg Tyr Lys Asn Ile Leu
                            520
                                            525
     Pro Phe Asp His Ser Arg Val Ile Leu Gln Gly Arg Asp Ser Asn Ile
10
                         535
     Pro Gly Ser Asp Tyr Ile Asn Ala Asn Tyr Ile Lys Asn Gln Leu Leu
           550
                              555
     Gly Pro Asp Glu Asn Ala Lys Thr Tyr Ile Ala Ser Gln Gly Cys Leu
15
                  565
                                   570
     Glu Ala Thr Val Asn Asp Phe Trp Gln Met Ala Trp Gln Glu Asn Ser
              580 585
     Arg Val Ile Val Met Thr Thr Arg Glu Val Glu Lys Gly Arg Asn Lys
                 600
      595
                                 605
     Cys Val Pro Tyr Trp Pro Glu Val Gly Met Gln Arg Ala Tyr Gly Pro
20
                          615
     Tyr Ser Val Thr Asn Cys Gly Glu His Asp Thr Thr Glu Tyr Lys Leu
         630
                                       635
     Arg Thr Leu Gln Val Ser Pro Leu Asp Asn Gly Asp Leu Ile Arg Glu
25
                                  650
     Ile Trp His Tyr Gln Tyr Leu Ser Trp Pro Asp His Gly Val Pro Ser
               660
                                665
                                                  670
     Glu Pro Gly Gly Val Leu Ser Phe Leu Asp Gln Ile Asn Gln Arg Gln
                             680
30
     Glu Ser Leu Pro His Ala Gly Pro Ile Ile Val His Cys Ser Ala Gly
                       695
                                           700
     Ile Gly Arg Thr Gly Thr Ile Ile Val Ile Asp Met Leu Met Glu Asn
                     710
                                       715
     Ile Ser Thr Lys Gly Leu Asp Cys Asp Ile Asp Ile Gln Lys Thr Ile
35
                  725 730 735
     Gln Met Val Arg Ala Gln Arg Ser Gly Met Val Gln Thr Glu Ala Gln
                                 745
     Tyr Lys Phe Ile Tyr Val Ala Ile Ala Gln Phe Ile Glu Thr Thr Lys
                             760
40
     Lys Lys Leu Glu Val Leu Gln Ser Gln Lys Gly Gln Glu Ser Glu Tyr
                          775
                                           780
     Gly Asn Ile Thr Tyr Pro Pro Ala Met Lys Asn Ala His Ala Lys Ala
                      790
                                        795
     Ser Arg Thr Ser Ser Lys His Lys Glu Asp Val Tyr Glu Asn Leu His
45
                  805
                                   810
     Thr Lys Asn Lys Arg Glu Glu Lys Val Lys Lys Gln Arg Ser Ala Asp
                                 825
               820
     Lys Glu Lys Ser Lys Gly Ser Leu Lys Arg Lys
           835
                             840
50
```

(2) INFORMATION FOR SEQ ID NO:118:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 2562 base pairs
- (B) TYPE: nucleic acid

(C) STRANDEDNESS: single

220

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

5

(A) NAME/KEY: Coding Sequence (B) LOCATION: 1...2559

(D) OTHER INFORMATION:

10 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:118:

			().	-,	DLQ	OENC	ב עב	SCRI	PTIC)N: 5	SEQ]	D NO):118	3:				
15	1			001	711;	5	y II	b bu	ені	S Ar	ng As 10	p Le	u Se	r Gl	y Le	u As _j 15	T GCA p Ala	48
	GA(G A	cc (CTG Leu	CTO Let 20	AAG Ly:	G GG G Gl	C CG y Ar	A GG g Gl	T GT y Va 25	I Hi	.C GG s Gl	T AG	C TTO	CTC Let 30	G GC	r CGG a Arg	96
20	CCC Pro	C AC		CGC Arg 85	AAC Lys	AA(CAC	G GG n Gl	T GA y As; 40	С TT p Ph	C TC e Se	G CT r Le	C TC u Se	C GT(r Va]	C AGO	GT(G GGG L Gly	144
25	GAT Asp	C C E O G I 50		TG al	ACC Thr	CAT His	ATT	CG(Arg 55	J Ile	C CA	G AA	C TC n Se	A GG r Gl	G GAI Y Asp	TTC Phe	TAT	GAC Asp	192
30	CTG Leu 65	TA	T G	GA ly	GGG Gly	GAG Glu	AAG Lys 70	TTT Phe	GCC Ala	G AC	r CT(3 AC	A GAO	G CTG	GTG Val	GAG Glu	TAC Tyr 80	240
35	TAC Tyr	AC Th	T C	AG ln	CAG Gln	CAG Gln 85	GGT Gly	GTC Val	CTC Leu	G CAC	GAC Asp 90	CGC Arg	C GAC J Asp	GGC Gly	ACC Thr	ATC Ile 95	ATC Ile	288
	CAC His	CT	CA uL _j	, –	TAC Tyr 100	CCG Pro	CTG Leu	AAC Asn	TGC Cys	Ser 105	Asp	CCC Pro	ACT Thr	AGT Ser	GAG Glu 110	AGG Arg	TGG Trp	336
40	TAC Tyr	CA:	F G(S G) 11	-1	CAC His	ATG Met	TCT Ser	GGC Gly	GGG Gly 120	CAG Gln	GCA Ala	GAG Glu	ACG Thr	CTG Leu 125	CTG Leu	CAG Gln	GCC Ala	384
45	AAG Lys	GG(Gl _y 130		AG (CCC Pro	TGG Trp	ACG Thr	TTT Phe 135	CTT Leu	GTG Val	CGT Arg	GAG Glu	AGC Ser 140	CTC Leu	AGC Ser	CAG Gln	CCT Pro	432
50	GGA Gly 145	GAC Asp	TI Ph	C (GTG /al	CTT Leu	TCT Ser 150	GTG Val	CTC Leu	AGT Ser	GAC Asp	CAG Gln 155	CCC Pro	AAG Lys	GCT Ala	GGC Gly	CCA Pro 160	480
55	GGC Gly	TCC Ser	CC Pr	G C		AGG Arg 165	GTC Val	ACC Thr	CAC His	ATC Ile	AAG Lys 170	GTC Val	ATG Met	TGC Cys	Glu	GGT Gly 175	GGA Gly	528
	CGC	TAC	AC.	A G	TG	GGT	GGT	TTG	GAG	ACC	TTC	GAC	AGC	CTC	ACG	GAC	CTG	576

										221							
	Arg	Tyr	Thr	Val 180	Gly	Gly	Leu	Glu	Thr 185	Phe	Asp	Ser	Leu	Thr 190	Asp	Leu	
5					AAG Lys												624
10					CAG Gln				_			_		_	_		672
					GTG Val										_		720
15					GGC Gly 245												768
20					TTG Leu												816
25					CGC Arg												864
30					GGA Gly												912
		_			ATC Ile									_		_	960
35					GCC Ala 325												1008
40					GCG Ala							_		_			1056
45					GAG Glu												1104
50					CAG Gln												1152
55					ACA Thr												1200
55	CCG	CTG	GAC	AAT	GGA	GAC	CTG	ATT	CGG	GAG	ATC	TGG	CAT	TAC	CAG	TAC	1248

										222							
	Pro	o Le	u As	p As	n Gl 40	y As _l 5	p Let	u Ile	e Ar	g Gl:		e Tr	рHi	в Ту	r Gl 41	n Tyr 5	
5	CT(Let	3 AG 1 Se	C TG r Tr	G CC p Pro 42	O AS	C CAT p His	r GG(s Gl)	G GTO	C CCC l Pro 425	Se:	r GA	G CC u Pr	T GG o Gl	G GG y Gl 43	y Va	C CTC l Leu	1296
10	AG(Sei	TT Ph	C CT e Le 43	u Asj	C CAC	G ATO	C AAC e Asr	C CAC n Glr 440	ı Arç	G CAC	G GAA	A AG	T CTO	u Pro	r CA	C GCA s Ala	1344
15	GGG	Pro) TT(C ATO	C GT0 ≥ Val	G CAC	C TGC Cys 455	Ser	GCC Ala	GGC Gly	C ATO	GGG Gly 460	y Ar	C AC	A GGG	C ACC	1392
	ATC Ile 465	110	r GT(≥ Val	C ATO	GAC Asp	ATG Met 470	Leu	ATG Met	GAG Glu	AAC Asn	ATC Ile	: Sei	C ACC	C AAC	G GG(C CTG Leu 480	1440
20	GAC Asp	TG7 Cys	GAC S Asp	C ATT	GAC Asp 485	ııe	CAG Gln	AAG Lys	ACC Thr	ATC Ile 490	Gln	ATC Met	GTC Val	CGC Arg	GCG Ala 495	G CAG	1488
25	CGC Arg	TCG	Gly	ATG Met	vai	CAG Gln	ACG Thr	GAG Glu	GCG Ala 505	CAG Gln	TAC Tyr	' AAG	TTC Phe	ATC	Tyr	GTG Val	1536
30	GCC Ala	ATC	GCC Ala 515	GIN	TTC Phe	ATT Ile	GAA Glu	ACC Thr 520	ACT Thr	AAG Lys	AAG Lys	AAG Lys	CTG Leu 525	GAG Glu	GTC Val	CTG Leu	1584
35	CAG Gln	TCG Ser 530	CAG Gln	AAG Lys	GGC Gly	CAG Gln	GAG Glu 535	TCG Ser	GAG Glu	TAC Tyr	GGG Gly	AAC Asn 540	ATC Ile	ACC Thr	TAT Tyr	CCC Pro	1632
	CCA Pro 545	GCC Ala	ATG Met	AAG Lys	AAT Asn	GCC Ala 550	CAT His	GCC Ala	AAG Lys	GCC Ala	TCC Ser 555	CGC Arg	ACC Thr	TCG Ser	TCC Ser	AAA Lys 560	1680
40	CAC His	AAG Lys	GAG Glu	GAT Asp	GTG Val 565	TAT Tyr	GAG Glu	AAC Asn	CTG Leu	CAC His 570	ACT Thr	AAG Lys	AAC Asn	AAG Lys	AGG Arg 575	GAG Glu	1728
45	GAG Glu	AAA Lys	GTG Val	AAG Lys 580	AAG Lys	CAG Gln	CGG Arg	TCA Ser	GCA Ala 585	GAC Asp	AAG Lys	GAG Glu	AAG Lys	AGC Ser 590	AAG Lys	GGT Gly	1776
50	TCC Ser	CTC Leu	AAG Lys 595	AGG Arg	AAG Lys	CGA Arg	He	CTG Leu 600	CAG Gln	TCG Ser	ACG Thr	GTA Val	CCG Pro 605	CGG Arg	GCC Ala	CGG Arg	1824
55	GAT Asp	CCA Pro 610	CCG Pro	GTC Val	GCC Ala	Thr	ATG Met 615	GTG Val	AGC Ser	AAG Lys	GGC Gly	GAG Glu 620	GAG Glu	CTG Leu	TTC Phe	ACC Thr	1872
	GGG (GTG	GTG	ccc	ATC	CTG	GTC (GAG	CTG	GAC	GGC	GAC	GTA	AAC	GGC	CAC	1920 222

	Gly 625	Val	Val	Pro	Ile	Leu 630	Val	Glu	Leu	Asp	Gly 635	Asp	Val	Asn	Gly	His 640	
5				GTG Val													1968
10				AAG Lys 660		_				_				_			2016
15				GTG Val													2064
15				CAC His													2112
20				GTC Val													2160
25				CGC Arg													2208
30				CTG Leu 740													2256
0.5				CTG Leu											_		2304
35				CAG Gln													2352
40				GAC Asp													2400
45	_		_	GGC Gly		_		_									2448
50				TCC Ser 820													2496
				CTG Leu													2544
55	GAC	GAG	CTG	TAC	AAG	TAA											2562 22

224

Asp Glu Leu Tyr Lys 850

55

5 (2) INFORMATION FOR SEQ ID NO:119: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 853 amino acids (B) TYPE: amino acid 10 (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: protein (v) FRAGMENT TYPE: internal 15 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:119: Met Leu Ser Arg Gly Trp Phe His Arg Asp Leu Ser Gly Leu Asp Ala 10 Glu Thr Leu Leu Lys Gly Arg Gly Val His Gly Ser Phe Leu Ala Arg 20 2.0 2.5 Pro Ser Arg Lys Asn Gln Gly Asp Phe Ser Leu Ser Val Arg Val Gly 40 Asp Gln Val Thr His Ile Arg Ile Gln Asn Ser Gly Asp Phe Tyr Asp 25 Leu Tyr Gly Gly Glu Lys Phe Ala Thr Leu Thr Glu Leu Val Glu Tyr 70 75 Tyr Thr Gln Gln Gln Gly Val Leu Gln Asp Arg Asp Gly Thr Ile Ile 85 90 His Leu Lys Tyr Pro Leu Asn Cys Ser Asp Pro Thr Ser Glu Arg Trp 30 100 105 Tyr His Gly His Met Ser Gly Gly Gln Ala Glu Thr Leu Leu Gln Ala 120 Lys Gly Glu Pro Trp Thr Phe Leu Val Arg Glu Ser Leu Ser Gln Pro 35 135 140 Gly Asp Phe Val Leu Ser Val Leu Ser Asp Gln Pro Lys Ala Gly Pro 150 155 Gly Ser Pro Leu Arg Val Thr His Ile Lys Val Met Cys Glu Gly Gly 165 170 Arg Tyr Thr Val Gly Gly Leu Glu Thr Phe Asp Ser Leu Thr Asp Leu 175 40 180 185 Val Glu His Phe Lys Lys Thr Gly Ile Glu Glu Ala Ser Gly Ala Phe 195 200 205 Val Tyr Leu Arg Gln Pro Tyr Tyr Ala Thr Arg Val Asn Ala Ala Asp 45 215 220 Ile Glu Asn Arg Val Leu Glu Leu Asn Lys Lys Gln Glu Ser Glu Asp 230 235 Thr Ala Lys Ala Gly Phe Trp Glu Glu Phe Glu Ser Leu Gln Lys Gln 245 250 Glu Val Lys Asn Leu His Gln Arg Leu Glu Gly Gln Arg Pro Glu Asn 50 260 265 Lys Gly Lys Asn Arg Tyr Lys Asn Ile Leu Pro Phe Asp His Ser Arg 280 285 Val Ile Leu Gln Gly Arg Asp Ser Asn Ile Pro Gly Ser Asp Tyr Ile

Asn Ala Asn Tyr Ile Lys Asn Gln Leu Leu Gly Pro Asp Glu Asn Ala

300

	305					310					315					320
	Lys	Thr	Tyr	Ile	Ala	Ser	Gln	Gly	Cys	Leu	Glu	Ala	Thr	Val	Asn	Asp
					325			_	_	330					335	_
	Phe	Trp	Gln	Met	Ala	Trp	Gln	Glu	Asn	Ser	Arq	Val	Ile	Val	Met	Thr
5		-		340		-			345		,			350		
	Thr	Ara	Glu	Val	Glu	Lvs	Glv	Ara		Lvs	Cvs	۷al	Pro		Trp	Pro
		5	355			-1-	1	360		-,-	-,		365	-7-		
	Glu	Val	Gly	Met	Gln	Ara	Δla		Glv	Pro	Tvr	Ser		Thr	Agn	Cvs
	014	370	U - y			5	375	- 7 -	- 1		-1-	380	V 4 1		11011	C, S
10	Glv		His	Asn	Thr	Thr	-	Tur	Twe	T.e.11	Δτα		T.e.u	Gln	Val	Ser
	385	014	1120	p		390	Olu		Lys	БСи	395	1111	шси	0111	va1	400
		I.a.ı	Asp	Acn	Glv		ĭ.e.ı	Tla) ra	Glu.		Trn	Wie	Tur	Gln	
	110	БСС	p	11011	405	пор	ncu		nr 9	410	110	ш	1112	T y L	415	- y -
	T.e.s	Car	Trp	Dro		Hie	Gly	Va l	Dro		Clu	Dro	Clv	Clar		Len
15	Deu	361	шр	420	Asp	1113	GIY	VAI	425	Ser	Giu	PIO	GIA	430	vai	ъęч
10	00*	Dho	T 011		Cln.	Tlo	7.00	C1 n		<i>0</i> 15	C1	C	T 0		11160	77-
	ser	PIIC	Leu 435	мар	GIII	116	ASII		Arg	GIII	GIU	ser		PIO	urs	Ala
	01	n		T1.	1707	***	C	440	27-	~1	T1 -	a 1	445	mb	a 1	m1
	GIA		Ile	TIE	vai	HIS		ser	АТА	GIY	тте		Arg	Thr	GIY	Thr
20	-1.	450	**- 3	- 7 -			455		~1	_	~ ,	460	_,	_	~ 3	_
20		11e	Val	тте	Asp		Leu	Met	Glu	Asn		Ser	Thr	ьys	Gly	
	465		_		_	470	~1	_			475			_		480
	Asp	Cys	Asp	тте	-	тте	GIn	ьуs	Thr		GIn	Met	Val	Arg		Gin
	_	_			485					490	_	_			495	
0.5	Arg	Ser	Gly		Val	Gln	Thr	Glu		GIn	Tyr	Lys	Phe		Tyr	Val
25				500					505					510		
	Ala	Ile	Ala	Gln	Phe	Ile	Glu		Thr	Lys	Lys	Lys		Glu	Val	Leu
			515	_				520					525			
	Gln		Gln	Lys	GTA	GIn		Ser	Glu	Tyr	Gly		Ile	Thr	Tyr	Pro
		530					535					540				
30	Pro	Ala	Met	Lys	Asn	Ala	His	Ala	Lys	Ala	Ser	Arg	Thr	Ser	Ser	-
	545					550					555					560
	His	Гуs	Glu	Asp		Tyr	Glu	Asn	Leu	His	Thr	ГÀг	Asn	Lys	Arg	Glu
					565					570					575	
	Glu	Lys	Val		Ъуs	Gln	Arg	Ser		Asp	Lys	Glu	Lys		Lys	Gly
35				580					585					590		
	Ser	Leu	Lys	Arg	Lys	Arg	Ile	Leu	Gln	Ser	Thr	Val	Pro	Arg	Ala	Arg
			595					600					605			
	Asp	Pro	Pro	Val	Ala	Thr	Met	Val	Ser	Lys	Gly	Glu	Glu	Leu	Phe	Thr
		610					615					620				
40	Gly	Val	Val	Pro	Ile	Leu	Val	Glu	Leu	Asp	Gly	Asp	Val	Asn	Gly	His
	625					630					635					640
	Lys	Phe	Ser	Val	Ser	Gly	Glu	Gly	Glu	Gly	Asp	Ala	Thr	Tyr	Gly	Lys
					645					650					655	
	Leu	Thr	Leu	Lys	Phe	Ile	Cys	Thr	Thr	Gly	Lys	Leu	Pro	Val	Pro	Trp
45				660					665					670		
	Pro	Thr	Leu	Val	Thr	Thr	Leu	Thr	Tyr	Gly	Val	Gln	Cys	Phe	Ser	Arg
			675					680					685			
	Tyr	Pro	Asp	His	Met	Lys	Gln	His	Asp	Phe	Phe	Lys	Ser	Ala	Met	Pro
		690					695					700				
50	Glu	Gly	Tyr	Val	Gln	Glu	Arg	Thr	Ile	Phe	Phe	Lys	Asp	Asp	Gly	Asn
	705					710					715					720
	Tyr	Lys	Thr	Arg	Ala	Glu	Val	Lys	Phe	Glu	Gly	Asp	Thr	Leu	Val	Asn
					725		-			730					735	
	Arg	Ile	Glu	Leu	Lys	Gly	Ile	Asp	Phe	Lys	Glu	Asp	Gly	Asn	Ile	Leu
55				740					745					750		
	Gly	His	Lys	Leu	Glu	Tyr	Asn	Tyr	Asn	Ser	His	Asn	Val	Tyr	Ile	Met

	226	
	755 760 765	
	Ala Asp Lys Gln Lys Asn Gly Ile Lys Val Asn Phe Lys Ile Arg His	
E	Asn Ile Glu Asp Gly Ser Val Gln Leu Ala Asp His Tyr Gln Gln Asn 785	
5		
	Thr Pro Ile Gly Asp Gly Pro Val Leu Leu Pro Asp Asn His Tyr Leu	
	Ser Thr Gln Ser Ala Leu Ser Lys Asp Pro Asn Glu Lys Arg Asp His	
10		
.0	Het var heu Leu Glu Phe Val Thr Ala Ala Gly Ile Thr Leu Gly Met	
	Asp Glu Leu Tyr Lys 845	
	850	
15	(2) INFORMATION FOR SEQ ID NO:120:	
	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 2994 base pairs (B) TYPE: nucleic acid	
20	(C) STRANDEDNESS: single	
	(D) TOPOLOGY: linear	
	(ii) MOLECULE TYPE: CDNA	
25	(ix) FEATURE:	
25	(A) MAMPIATOR TO A	
	(A) NAME/KEY: Coding Sequence (B) LOCATION: 12991	
	(D) OTHER INFORMATION:	
30	(xi) SEQUENCE DECORPORA	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:120:	
	ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG Met Val Ser Lys Gly Gly Law 21 Acc GGG GTG GTG CCC ATC CTG 4	•
	1 I gid Gid Leu Phe Thr Gly Val Val Pro Ile Leu	В
35	10 15	
	GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC Val Glu Leu Asp Gly Asp Cal App Gly Will App	_
	20 Ash Gly His Lys Phe Ser Val Ser Gly	ь
40	25 30	
40	GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC 144	4
	25 Mid In Tyl Gly Lys Leu Thr Leu Lys Phe Ile	*
	40 45	
45	TGC ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC Cys Thr Thr Gly Lys Leu Pro Vol Pro TG	,
	50 FF FO Trp Pro Thr Leu Val Thr Thr	•
	55 60	
	CTG ACC TAC GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG AAG Leu Thr Tyr Gly Val Glr Cyc Pha Gar Tac CCC GAC CAC ATG AAG 240	1
50	65 To The Ser Arg Tyr Pro Asp His Met Lys	
	75 80	
	CAG CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG Gln His Asp Phe Phe Lyg Sor Ale Man To GAA GGC TAC GTC CAG GAG 288	
	as Sel Ala Met Pro Glu Gly Tyr Val Glu	
55	90 95	
	CGC ACC ATC TTC TTC AAG GAC GAC GGC AAC TAC AAG ACC CGC GCC GAG 336	
	336	226
		220

										227								
	Arg	Thr	Ile	Phe 100	Phe	Lys	Asp	Asp	Gly 105	Asn	Tyr	Lys	Thr	Arg 110	Ala	Glu		
5												ATC Ile					384	
10												CAC His 140			_		432	
												GAC Asp					480	•
												ATC Ile	_			_	528	l
20												CCC Pro					57€	i
25												ACC Thr					624	•
30												GTC Val 220					672	!
35												GAG Glu					720)
33												ACC Thr		_		_	768	3
40												GAG Glu					816	5
45												TAC Tyr					864	ł
50												CTA Leu 300					912	2
55												ATT Ile					960)
55	AAC	CAT	GCC	AAT	GTT	GTA	AAG	GCC	TGT	GAT	GTT	CCT	GAA	GAA	TTG	AAT	1008	3 2:

										228							
	As	n H	is A	la As	sn Va 32	l Va	1 Ьу	rs Al	la Cy	s As	p Va 0	l Pr	o Gl	.u G]		eu As 35	n
5				34	0	p va	I FL	O LLE	и Le 34	u Al 5	a Me	t Gl	и Ту	r Cy 35	s Se	CT GG er Gl	У
10	GG. Gl	A GA y As	AT CI Sp Le 35		A AA g Ly	G CTO	G CT u Le	C AA u As 36	и гА	A CC. s Pr	A GA.	A AA u As	T TG n Cy 36	s Cy	T GO	SA CT	T 1104 u
15	AA) Lys	A GA s Gl 37		C CA	G AT	A CT:	TC 1 Se: 37!	т те	A CTA	A AG	r GA'	T AT	e Gly	G TC y Se	T GG r Gl	G AT	Г 1 15 2
	CG/ Arg 385	A TA g Ty	T TT r Le	G CA u Hi	T GAA	A AAC 1 Asr 390	r ny:	A AT	T ATA	A CAT	CGA 3 Arc	J Ası	r CTA	A AA	A CC s Pr	T GAZ O Glu 400	1
20	AAC Asn	AT.	A GT e Va	r CT l Lei	F CAC 1 Glr 405	. Ash	' GTT	GGT Gly	r GGA 7 Gly	AAG Lys	Ile	ATA	A CAT	AAA Lys	A AT. 5 Il 41	A ATT e Ile 5	. 1248
25	GAT Asp	CTC	G GGA	A TAT 7 Ty: 420	. Ala	AAA Lys	GAT Asp	GTT Val	GAT Asp 425	GIn	GGA Gly	AGT Ser	CTG	TGT Cys	Th	A TCT r Ser	1296
30	TTT Phe	Va]	G GG# 1 Gly 435		CTG	CAG Gln	TAT Tyr	CTG Leu 440	Ата	CCA Pro	GAG Glu	CTC Leu	TTT Phe 445	GAG Glu	AA7 Asr	r AAG 1 Lys	1344
35	CCT Pro	TAC Tyr 450		GCC Ala	ACT Thr	GTT Val	GAT Asp 455	TAT Tyr	TGG Trp	AGC Ser	TTT Phe	GGG Gly 460	ACC Thr	ATG Met	GTA Val	TTT Phe	1392
	GAA Glu 465	TGT Cys	'ATT	GCT Ala	GGA Gly	TAT Tyr 470	AGG Arg	CCT Pro	TTT Phe	TTG Leu	CAT His 475	CAT His	CTG Leu	CAG Gln	CCA Pro	TTT Phe	1440
40	ACC Thr	TGG Trp	CAT His	GAG Glu	AAG Lys 485	ATT Ile	AAG Lys	AAG Lys	AAG Lys	GAT Asp 490	CCA Pro	AAG Lys	TGT Cys	ATA Ile	TTT Phe 495	GCA Ala	1488
45	TGT Cys	GAA Glu	GAG Glu	ATG Met 500	TCA Ser	GGA Gly	GAA Glu	GTT Val	CGG Arg 505	TTT Phe	AGT Ser	AGC Ser	CAT His	TTA Leu 510	CCT Pro	CAA Gln	1536
50	CCA Pro	AAT Asn	AGC Ser 515	CTT Leu	TGT Cys	AGT Ser	Leu	ATA Ile 520	GTA Val	GAA Glu	CCC Pro	Met	GAA Glu 525	AAC Asn	TGG Trp	CTA Leu	1584
55	CAG Gln	TTG Leu 530	ATG Met	TTG Leu	AAT Asn	TTD A	GAC Asp 535	CCT Pro	CAG Gln	CAG .	Arg	GGA Gly 540	GGA Gly	CCT Pro	GTT Val	GAC Asp	1632
	CTT	ACT	TTG	AAG	CAG (CCA 1	AGA '	TGT	TTT (GTA '	TTA Z	ATG (GAT (CAC	ATT	TTG	1680 228

	Leu 545	Thr	Leu	Lys	Gln	Pro 550	Arg	Cys	Phe	Val	Leu 555	Met	Asp	His	Ile	Leu 560	
5							_						_		ATA Ile 575		1728
10														_	TCT Ser		1776
15															CTT Leu		1824
15															TGT Cys		1872
20															TTT Phe		1920
25															TTA Leu 655		1968
30						_							_		CCA Pro	_	2016
35						_									TCT Ser		2064
50															GCA Ala		2112
40															AAC Asn		2160
45															TTT Phe 735	_	2208
50															ACG Thr		2256
55															GAA Glu		2304
	AAG	GCC	ATC	CAC	TAT	GCT	GAG	GTT	GGT	GTC	ATT	GGA	TAC	CTG	GAG	GAT	2352

										250							
	Ly	s Al 77	a I] 0	е ні	s Ту	r Ala	a Gli 77!	u Va 5	l Gl	y Va	1 11	e Gl 78		r Le	u Gl	u Asp	
5	CA(Gl: 785		T AI e Me	TG TC	T TT	G CAT u His 790	AT &	r ga a Gl	A AT u Il	C AT e Me	G GG t G1 79	y Le	A CA	G AA n Ly	G AG s Se	C CCC r Pro 800	2400
10	TAT Ty1	r GG.	A AG y Ar	A CG g Ar	T CAG g Gli 809	п Сту	GAC Asp	TTO Let	G ATO	G GA t Gl: 81	u Se	T CTO	G GA	A CA	G CG n Ar 81	T GCC g Ala 5	2448
15	ATT Ile	GA' As	r CT	A TA' u Ty: 82	г гу	G CAG	TTA Leu	AAi Lys	A CAC S His 825	s Arg	A CC	T TC	A GAT	CAC His	s Se	C TAC r Tyr	2496
	AGT Ser	' GA(2 AG 2 Se: 83!		A GAG	ATG Met	GTG Val	AA/ Lys 840	3 I16	E ATT	GTC Val	G CAC	C ACT	· Val	G CAG	G AGT n Ser	2544
20	CAG Gln	GAC Asp 850		r GTO	CTC Leu	AAG Lys	GAG Glu 855	CTC	TTT Phe	GGT Gly	CAT His	TTC Leu 860	Ser	AAC Lys	TTC Lev	TTG	2592
25	GGC Gly 865	TGT Cys	AAC Lys	G CAG	AAG Lys	ATT Ile 870	ATT Ile	GAT Asp	CTA Leu	CTC Leu	CCT Pro 875	Lys	GTG Val	GAA Glu	GTG Val	GCC Ala 880	2640
30	CTC Leu	AGT Ser	AAT Asn	ATC	AAA Lys 885	GAA Glu	GCT Ala	GAC Asp	AAT Asn	ACT Thr 890	GTC Val	ATG Met	TTC Phe	ATG Met	CAG Gln 895	Gly	2688
35	AAA Lys	AGG Arg	CAG Gln	AAA Lys 900	GAA Glu	ATA Ile	TGG Trp	CAT His	CTC Leu 905	CTT Leu	AAA Lys	ATT Ile	GCC Ala	TGT Cys 910	ACA Thr	CAG Gln	2736
	AGT Ser	TCT Ser	GCC Ala 915	CGC Arg	TCT Ser	CTT Leu	GTA Val	GGA Gly 920	TCC Ser	AGT Ser	CTA Leu	GAA Glu	GGT Gly 925	GCA Ala	GTA Val	ACC Thr	2784
40	CCT Pro	CAG Gln 930	ACA Thr	TCA Ser	GCA Ala	TGG Trp	CTG Leu 935	CCC Pro	CCG Pro	ACT Thr	TCA Ser	GCA Ala 940	GAA Glu	CAT His	GAT Asp	CAT His	2832
45	TCT Sér 945	CTG Leu	TCA Ser	TGT Cys	vaı	GTA / Val ' 950	ACT Thr	CCT Pro	CAA Gln	GAT Asp	GGG Gly 955	GAG Glu	ACT Thr	TCA Ser	GCA Ala	CAA Gln 960	2880
50	ATG . Met	ATA Ile	GAA Glu	GAA Glu	AAT Asn 965	TTG /	AAC (Asn (TGC Cys	CTT Leu	GGC Gly 970	CAT His	TTA Leu	AGC Ser	ACT Thr	ATT Ile 975	ATT Ile	2928
55	CAT (GAG Glu	GCA Ala	AAT Asn 980	GAG Glu	GAA (Glu (CAG (GGC Gly	AAT Asn 985	AGT Ser	ATG Met	ATG Met	Asn	CTT Leu 990	GAT Asp	TGG Trp	2976
-	AGT T	rgg	TTA	ACA	GAA '	TGA											2994 230

231

Ser Trp Leu Thr Glu 995

5 (2) INFORMATION FOR SEQ ID NO:121:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 997 amino acids
 - (B) TYPE: amino acid
- 10 (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
 - (ii) MOLECULE TYPE: protein
 - (v) FRAGMENT TYPE: internal

15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:121:

	Met 1	Val	Ser	Lys	Gly 5	Glu	Glu	Leu	Phe	Thr 10	Gly	Val	Val	Pro	Ile 15	Leu
20	Val	Glu	Leu	Asp 20	Gly	Asp	Val	Asn	Gly 25	His	Lys	Phe	Ser	Val 30	Ser	Gly
		Gly	35					40					45			
25	Cys	Thr 50	Thr	Gly	Lys	Leu	Pro 55	Val	Pro	Trp	Pro	Thr 60	Leu	Val	Thr	Thr
	65	Thr		_		70	_			_	75		~			80
	Gln	His	Asp	Phe	Phe 85	Lys	Ser	Ala	Met	Pro 90	Glu	Gly	Tyr	Val	Gln 95	Glu
30	_	Thr		100		-	_	_	105		-	-		110		
	Val	Lys	Phe 115	Glu	Gly	Asp	Thr	Leu 120	Val	Asn	Arg	Ile	Glu 125	Leu	Lys	Gly
35		Asp 130		-		-	135				-	140	-			-
	Asn 145	Tyr	Asn	Ser	His	Asn 150	Val	Tyr	Ile	Met	Ala 155	Asp	Lys	Gln	Lys	Asn 160
	Gly	Ile	Lys	Val	Asn 165	Phe	Lys	Ile	Arg	His 170	Asn	Ile	Glu	Asp	Gly 175	Ser
40	Val	Gln	Leu	Ala 180	Asp	His	Tyr	Gln	Gln 185	Asn	Thr	Pro	Ile	Gly 190	qaA	Gly
	Pro	Val	Leu 195	Leu	Pro	Asp	Asn	His 200	Tyr	Leu	Ser	Thr	Gln 205	Ser	Ala	Leu
45	Ser	Lys 210	Asp	Pro	Asn	Glu	Lys 215	Arg	Asp	His	Met	Val 220	Leu	Leu	Glu	Phe
	Val 225	Thr	Ala	Ala	Gly	Ile 230	Thr	Leu	Gly	Met	Asp 235	,	Leu	Tyr	Lys	Ser 240
	Gly	Leu	Arg	Ser	Arg 245	Ala	Gln	Ala	Ser	Asn 250	Ser	Thr	Met	Glu	Arg 255	Pro
50	Pro	Gly	Leu	Arg 260	Pro	Gly	Ala	Gly	Gly 265	Pro	Trp	Glu	Met	Arg 270	Glu	Arg
	Leu	Gly	Thr 275	Gly	Gly	Phe	Gly	Asn 280	Val	Cys	Leu	Tyr	Gln 285	His	Arg	Glu
55	Leu	Asp 290	Leu	Lys	Ile	Ala	Ile 295	Lys	Ser	Cys	Arg	Leu 300	Glu	Leu	Ser	Thr

Lys Asn Arg Glu Arg Trp Cys His Glu Ile Gln Ile Met Lys Lys Leu

											232	2							
)5				3	10					3	15						
	As	sn H	is A	la A	sn V 3	al V 25	al I	ys	Al	а Су	s As	p Va	al P	ro (Glu	Gl			320 Asn
5	13	e L	eu I	le H.	is A	sp V	al I	ro	Le	u Le	u Al	a Me	et G	lu 7	Гуr	СУ	33 S Se	35 er	Gly
	G1	y A	sp L	eu A: 55		ys L	eu I	eu	Ası	34 n Ly	s Pr	o G	u As	sn (:ys	35 Cy	0 s G]	У	Leu
		s G		er G			eu S	er	301					_					
10			_	eu Hi		lu A	sn L	12					~ ~ ~	• •					
				al Le															
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				-					440						A =				
20			-	r Al			4	22						^					
20	465	т Су	s II	e Al	a Gl	у Ту	r A	rg	Pro	Phe	Lei	ı Hi	s Hi	s L	eu	Gln	Pro	o E	Phe
				s Gl															
25				u Me 50													Pro	o G	
									コノロ						lu	Asn	Trp		
20			-	t Le									- 4 /	/ G]	-у				
30	_			u Lys		33	v						Met	As					
				s Ile								Thr	Ser					Ι	le
35				1 Leu 580							Leu	His					Ser	A	
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40				/ Ile										Se	r				
40				Val									Val	Ty					
				Thr								Ala						Se	
45				Asn 660							Ser								
									la (Glu					r V				
	Leu	Lys 690	Glu	Asp	Tyr	Ser	Arc 695	L	eu :	Phe	Gln	Gly	Gln	685 Arg	j A	la.	Ala	Me	t
50				Leu			Asn	A.											
				Ala		Gln	Glr												s
55	Lys				Leu					Arg						et '			
	Gly	Ile	Ser	Ser	Glu	Lys	Met	Le	eu I	yys :	Ala	Trp	Lys	Glu	7: Me	50 et (Glu	Gl:	u

			755					760					765					
	Lys	Ala 770	Ile	His	Tyr	Ala	Glu 775	Val	Gly	Val	Ile	Gly 780	Tyr	Leu	Glu	Asp		
	Gln	Ile	Met	Ser	Leu	His		Glu	Ile	Met	Gly		Gln	Lys	Ser	Pro		
5	785					790					795					800		
	Tyr	Gly	Arg	Arg	Gln 805	Gly	Asp	Leu	Met	Glu 810	Ser	Leu	Glu	Gln	Arg 815	Ala		
	Ile	Asp	Leu	Tyr 820	Lys	Gln	Leu	Lys	His 825	Arg	Pro	Ser	Asp	His 830	Ser	Tyr		
10	Ser	Asp	Ser 835	Thr	Glu	Met	Val	Lys 840		Ile	Val	His	Thr 845		Gln	Ser		
	Gln	Asp 850		Val	Leu	Lys	Glu 855		Phe	Gly	His	Leu 860	Ser	Lys	Leu	Leu		
	Glv		Lvs	Gln	Lvs	Tle		Asp	Len	Len	Pro			Glu	Val	Δla		
15	865	0,0	_,,	~	_,,	870				Dea	875	2,5	V (1, 1		***	880		
	Leu	Ser	Asn	Ile	-	Glu	Ala	Asp	Asn		Val	Met	Phe	Met	Gln	Gly		
	*	•	03	•	885	T 2 -	m	***		890	-	-7.			895	a 1.		
	-	_		900					905		-			910	Thr			
20	Ser	Ser	Ala 915	Arg	Ser	Leu	Val	Gly 920	Ser	Ser	Leu	Glu	Gly 925	Ala	Val	Thr		
	Pro	Gln 930	Thr	Ser	Ala	Trp	Leu 935	Pro	Pro	Thr	Ser	Ala 940	Glu	His	Asp	His		
0.5		Leu	Ser	Cys	Val		Thr	Pro	Gln	Asp		Glu	Thr	Ser	Ala			
25	945	т] -	G1	01	»	950	7		T ====	01	955	T	~	mla sa	T10	960		
	мес	11e	GIU	Glu	965	Leu	ASN	Cys	ren	970	Hls	Leu	ser	Thr	11e 975	11e		
	His	Glu	Ala		Glu	Glu	Gln	Gly		Ser	Met	Met	Asn		Asp	Trp		
30	Ser	Trp	Leu 995	980 Thr	Glu				985					990				
				INI	EODM?	יתרתי	J FOI	o e E/	חז ר	NO.	122.							
			(2)	1141	CRI	11101	v FOI	C SE	מו ג	NO:	122:							
35		(:	i) sı	EQUE	VCE (CHARA	CTE	RIST	ICS:									
				LENG				_	airs									
				TYPI														
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40																		
				OLEC		TYPE	E: cl	ANC										
			(A)	NAN	ME/KI	EY: (Codi	ng Se	equei	nce								
45				LO														
			. (D)	OTI	HER .	LNPOR	KMAT.	LON:										
		()	ci) S	EQUI	ENCE	DESC	CRIP	rion	: SE	Q ID	NO:	122:						
50	ATG	GAG	CGG	CCC	CCG	GGG	CTG	CGG	CCG	GGC	GCG	GGC	GGG	CCC	TGG	GAG	4	18
		Glu	Arg	Pro		Gly	Leu	Arg	Pro	_	Ala	Gly	Gly	Pro	Trp	Glu		
	1				5					10					15			
															CTG		9	96
55	Met	Arg	Glu	Arg 20	Leu	Gly	Thr	Gly	Gly 25	Phe	Gly	Asn	Val	Cys 30	Leu	Tyr		
				20					23									

5	CAG Gln	CAT His	CGG Arg	GAA Glu	CTT Leu	GAT Asp	CTC Leu	AAA Lys 40	ATA Ile	GCA Ala	ATT	' AAG	TCT Ser 45	TGT Cys	CGC Arg	CTA Leu	144
3	GAG Glu	CTA Leu 50	AGT Ser	ACC Thr	AAA Lys	AAC Asn	AGA Arg 55	GAA Glu	CGA Arg	TGG Trp	TGC Cys	CAT His 60	GAA Glu	ATC Ile	CAG Gln	ATT	192
10	ATG Met 65	AAG Lys	AAG Lys	TTG Leu	AAC Asn	CAT His 70	GCC Ala	AAT Asn	GTT Val	GTA Val	AAG Lys 75	GCC Ala	TGT Cys	GAT Asp	GTT Val	CCT Pro 80	240
15	Glu	Glu	Leu	Asn	Ile 85	TTG Leu	Ile	His	Asp	Val 90	Pro	Leu	Leu	Ala	Met 95	Glu	288
20	Tyr	Cys	Ser	Gly 100	Gly	GAT Asp	Leu	Arg	Lys 105	Leu	Leu	Asn	Lys	Pro 110	Glu	Asn	336
25	Cys	Cys	Gly 115	Leu	Lys	GAA Glu	Ser	Gln 120	Ile	Leu	Ser	Leu	Leu 125	Ser	Asp	Ile	384
	Gly	Ser 130	Gly	Ile	Arg	TAT Tyr	Leu 135	His	Glu	Asn	Lys	Ile 140	Ile	His	Arg	Asp	432
30	CTA Leu 145	AAA Lys	CCT Pro	GAA Glu	AAC Asn	ATA Ile 150	GTT Val	CTT Leu	CAG Gln	GAT Asp	GTT Val 155	GGT Gly	GGA Gly	AAG Lys	ATA Ile	ATA Ile 160	480
35	CAT His	AAA Lys	ATA Ile	ATT Ile	GAT Asp 165	CTG Leu	GGA Gly	TAT Tyr	GCC Ala	AAA Lys 170	GAT Asp	GTT Val	GAT Asp	CAA Gln	GGA Gly 175	AGT Ser	528
40	CTG Leu	TGT Cys	ACA Thr	TCT Ser 180	TTT Phe	GTG Val	GGA Gly	ACA Thr	CTG Leu 185	CAG Gln	TAT Tyr	CTG Leu	GCC Ala	CCA Pro 190	GAG Glu	CTC Leu	576
45	TTT Phe	GAG Glu	AAT Asn 195	AAG Lys	CCT Pro	TAC Tyr	ACA Thr	GCC Ala 200	ACT Thr	GTT Val	GAT Asp	TAT Tyr	TGG Trp 205	AGC Ser	TTT Phe	GGG Gly	624
	ACC Thr	ATG Met 210	GTA Val	TTT Phe	GAA Glu	TGT Cys	ATT Ile 215	GCT Ala	GGA Gly	TAT Tyr	AGG Arg	CCT Pro 220	TTT Phe	TTG Leu	CAT His	CAT His	672
50	CTG Leu 225	CAG Gln	CCA Pro	TTT Phe	Thr	TGG Trp 230	CAT His	GAG Glu	AAG Lys	ATT Ile	AAG Lys 235	AAG Lys	AAG Lys	GAT Asp	CCA Pro	AAG Lys 240	720
55	TGT Cys	ATA Ile	TTT Phe	GCA Ala	TGT Cys 245	GAA Glu	GAG Glu	ATG Met	TCA Ser	GGA Gly 250	GAA Glu	GTT Val	CGG Arg	TTT Phe	AGT Ser 255	AGC Ser	768

			AAT Asn						816
5			TTG Leu						864
10			ACT Thr						912
15			TTG Leu 310						960
20			TTT Phe						1008
25			GAG Glu						1056
			ACA Thr						1104
30			GAT Asp						1152
35			AGT Ser 390						1200
40			TGT Cys						1248
45			CAG Gln						1296
			AAA Lys						1344
50	_		AGT Ser						1392
55			ATC Ile 470						1440

	GAG Glu	TTT Phe	TTT	CAC His	AAA Lys	. AGC Ser	ATT	CAG	CTT Leu	GAC Asp	TTG	GAG	AGA Arq	TAC	AGC Ser	GAG	1488
5					485					490			3	-7-	495		
	CAG Gln	ATC Met	ACG Thr	TAT Tyr 500	GGG	ATA Ile	TCT Ser	TCA Ser	GAA Glu 505	Lys	ATG Met	CTA Leu	AAA Lys	GCA Ala 510	TGG Trp	AAA Lys	1536
10	GAA Glu	ATG Met	GAA Glu 515	Glu	AAG Lys	GCC Ala	ATC Ile	CAC His 520	TAT Tyr	GCT Ala	GAG Glu	GTT Val	GGT Gly 525	GTC Val	ATT Ile	GGA Gly	1584
15	TAC Tyr	CTG Leu 530	Glu	GAT Asp	CAG Gln	ATT Ile	ATG Met 535	Ser	TTG Leu	CAT His	GCT Ala	GAA Glu 540	ATC Ile	ATG Met	GGG Gly	CTA Leu	1632
20	CAG Gln 545	AAG Lys	AGC Ser	CCC	TAT Tyr	GGA Gly 550	AGA Arg	CGT Arg	CAG Gln	GGA Gly	GAC Asp 555	TTG Leu	ATG Met	GAA Glu	TCT Ser	CTG Leu 560	1680
25	GAA Glu	CAG Gln	CGT Arg	GCC Ala	ATT Ile 565	GAT Asp	CTA Leu	TAT Tyr	AAG Lys	CAG Gln 570	TTA Leu	AAA Lys	CAC His	AGA Arg	CCT Pro 575	TCA Ser	1728
	GAT Asp	CAC His	TCC Ser	TAC Tyr 580	AGT Ser	GAC Asp	AGC Ser	ACA Thr	GAG Glu 585	ATG Met	GTG Val	AAA Lys	ATC Ile	ATT Ile 590	GTG Val	CAC His	1776
30	ACT Thr	GTG Val	CAG Gln 595	AGT Ser	CAG Gln	GAC Asp	CGT Arg	GTG Val 600	CTC Leu	AAG Lys	GAG Glu	CTG Leu	TTT Phe 605	GGT Gly	CAT His	TTG Leu	1824
35	AGC Ser	AAG Lys 610	TTG Leu	TTG Leu	GGC Gly	TGT Cys	AAG Lys 615	CAG Gln	AAG Lys	ATT Ile	ATT Ile	GAT Asp 620	CTA Leu	CTC Leu	CCT Pro	AAG Lys	1872
40	GTG Val 625	GAA Glu	GTG Val	GCC Ala	CTC Leu	AGT Ser 630	AAT Asn	ATC Ile	AAA Lys	GAA Glu	GCT Ala 635	GAC Asp	AAT Asn	ACT Thr	GTC Val	ATG Met 640	1920
45	TTC Phe	ATG Met	CAG Gln	GGA Gly	AAA Lys 645	AGG Arg	CAG Gln	AAA Lys	GAA Glu	ATA Ile 650	TGG Trp	CAT His	CTC Leu	CTT Leu	AAA Lys 655	ATT Ile	1968
	GCC Ala	TGT Cys	ACA Thr	CAG Gln 660	AGT Ser	TCT Ser	GCC Ala	CGC Arg	TCT Ser 665	CTT Leu	GTA Val	GGA Gly	TCC Ser	AGT Ser 670	CTA Leu	GAA Glu	2016
50	GGT Gly	GCA Ala	GTA Val 675	ACC Thr	CCT Pro	CAG Gln	ACA Thr	TCA Ser 680	GCA Ala	TGG Trp	CTG Leu	Pro	CCG Pro 685	ACT Thr	TCA Ser	GCA Ala	2064
55	GAA Glu	CAT His 690	GAT Asp	CAT His	TCT Ser	Leu	TCA Ser 695	TGT Cys	GTG Val	GTA Val	ACT Thr	CCT Pro 700	CAA Gln	GAT Asp	GGG Gly	GAG Glu	2112

5			ATG Met						2160
J			CAT His 725						2208
10			AGT Ser						2256
15			ACC Thr						2304
20			CTG Leu						2352
25			GGC Gly						2400
			ATC Ile 805						2448
30			ACC Thr						2496
35			AAG Lys						2544
40			GAG Glu						2592
45			GAG Glu						2640
			GGC Gly 885						2688
50			TAC Tyr						2736
55			AAC Asn						2784

5		93	0	ib Gi	y se	r va	93	n Le	u Al	a As	p Hi	s Ty 94	r Gl O	n Gl	n As	C ACC	•
	Pr 94	0 11	e Gl	y As	p Gl	y Pr	o Va	G CT l Le	G CT u Le	G CC u Pr	C GA O As 95	p As:	C CA n Hi	C TA s Ty	C CI r Le	G AGO u Ser 960	:
10	***	1 91	11 56	I AI	а Беі 96!	ı se:	г цу	s As	p Pr	O As 97	n Gli 0	л ГА	s Ar	g As	р Ні 97	_	
15	va	т Бе	и ље	u G1	u Phe O	e Va.	AC LTh:	C GC r Al	C GC a Al 98	a Gl	G ATO	C ACT	r CTC	GG(1 Gly 99(y Me	G GAC t Asp	2976
20		u Lei		r Ly:	G TAZ	A											2991
25		•	(i) S (A) (B)	EQUI LEN	NFORM ENCE IGTH: PE: a RANDE	CHAR 996 mino	ACTE ami aci	ERIST .no a	rics:		123:						
30		((D) ii) v) F	TOP MOLE	OLOG CULE	Y: 1 TYP TYPE	inea E: p : in	rote	in al								
35	Met 1				Pro						NO: Ala		Gly	Pro	Trp	Glu	
	Met			20					25		Gly			3.0			
40			22					40			Ile		45	Суѕ			
		50					55				Cys	60					
45						70					Lys 75					9.0	
					85					90	Pro				0 E		
50				100					105		Leu			210			
50			112					120			Ser		125				
		130					135				Lys	140	Ile				
55	-15					T20					Val 155					100	
	His	Lys	Ile	Ile	Asp	Leu	Gly	Tyr	Ala	Lys	Asp	Val	Asp	Gln	Gly	160 Ser	

					165					170					175	
	Leu	Cvs	Thr	Ser		Val	Glv	Thr	Leu		Tvr	Leu	Ala	Pro		Leu
		-,-		180					185		-1-			190		
5	Phe	Glu	Asn 195	Lys	Pro	Tyr	Thr	Ala 200	Thr	Val	qaA	Tyr	Trp 205	Ser	Phe	Gly
	Thr	Met 210	Val	Phe	Glu	Cys	Ile 215	Ala	Gly	Tyr	Arg	Pro 220	Phe	Leu	His	His
	Leu 225	Gln	Pro	Phe	Thr	Trp 230	His	Glu	Lys	Ile	Lys 235	Lys	Lys	qaA	Pro	Lys 240
10	Cys	Ile	Phe	Ala	Cys 245	Glu	Glu	Met	Ser	Gly 250	Glu	Val	Arg	Phe	Ser 255	Ser
				Gln 260					265					270		
15	Glu	Asn	Trp 275	Leu	Gln	Leu	Met	Leu 280	Asn	Trp	Asp	Pro	Gln 285	Gln	Arg	Gly
	-	290		Asp			295	_			_	300				
	305			Leu		310	_				315					320
20		•		Ile	325					330	_				335	
				Arg 340			_		345	-				350		
25			355	Ser			_	360			_		365	_		
		370	_	Val			375			_	_	380		_		
20	385			Asp		390					395					400
30	-			Ser	405				_	410			-		415	
				Ile 420 Gly				_	425		_			430		
35			435	Met				440					445			
		450		Thr			455					460				
	465	ביים			200	470	501		DCI	01	475	Deu	_,_		-1-	480
40	Glu	Phe	Phe	His	Lys 485	Ser	Ile	Gln	Leu	Asp 490	Leu	Glu	Arg	Tyr	Ser 495	Glu
				Tyr 500	_				505	_			_	510		
45			515	Glu	-			520	-				525			
	_	530		Asp			535					540				
50	545	-		Pro	_	550	_	_		_	555					560
50			-	Ala	565				_	570		_			575	
				Tyr 580					585					590		
55			595	Ser				600					605			
	ser	пÀг	ьeu	Leu	GIA	Cys	пàв	GIN	гÀв	тте	тте	Asp	ոեն	Leu	PLO	nys

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615
                                                620
      Val Glu Val Ala Leu Ser Asn Ile Lys Glu Ala Asp Asn Thr Val Met
                      630
                                 635
      Phe Met Gln Gly Lys Arg Gln Lys Glu Ile Trp His Leu Leu Lys Ile
 5
                     645
                                       650
      Ala Cys Thr Gln Ser Ser Ala Arg Ser Leu Val Gly Ser Ser Leu Glu
                 660
                                   665
      Gly Ala Val Thr Pro Gln Thr Ser Ala Trp Leu Pro Pro Thr Ser Ala
                                680
                                                   685
10
      Glu His Asp His Ser Leu Ser Cys Val Val Thr Pro Gln Asp Gly Glu
                         695
                                               700
      Thr Ser Ala Gln Met Ile Glu Glu Asn Leu Asn Cys Leu Gly His Leu
                        710
                                           715
      Ser Thr Ile Ile His Glu Ala Asn Glu Glu Gln Gly Asn Ser Met Met
15
                  725
                                       730
      Asn Leu Asp Trp Ser Trp Leu Thr Glu Trp Val Pro Arg Ala Arg Asp
                         745
      Pro Pro Val Ala Thr Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly
                                760
20
      Val Val Pro Ile Leu Val Glu Leu Asp Gly Asp Val Asn Gly His Lys
                            775
      Phe Ser Val Ser Gly Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu
                        790
                                           795
      Thr Leu Lys Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro
25
                    805
                                       810
      Thr Leu Val Thr Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr
                820
                                    825
                                                830
      Pro Asp His Met Lys Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu
                               840
30
     Gly Tyr Val Gln Glu Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr
                           855
                                              860
     Lys Thr Arg Ala Glu Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg
                        870
                                          875
     Ile Glu Leu Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly
35
                    885
                                       890
     His Lys Leu Glu Tyr Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala
                                   905
     Asp Lys Gln Lys Asn Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn
                               920
                                     925
40
     Ile Glu Asp Gly Ser Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr
                           935
                                               940
     Pro Ile Gly Asp Gly Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser
                        950
                                          955
     Thr Gln Ser Ala Leu Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met
45
                    965
                                       970
     Val Leu Leu Glu Phe Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp
             980
                                    985
     Glu Leu Tyr Lys
             995
50
```

(2) INFORMATION FOR SEQ ID NO:124:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 1908 base pairs
- 55 (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single

241

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

5

15

35

55

(A) NAME/KEY: Coding Sequence

(B) LOCATION: 1...1905

(D) OTHER INFORMATION:

10 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:124:

ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG

Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
20 25 30

20 GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC
Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
35 40 45

TGC ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC

25 Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr

50 55 60

CTG ACC TAC GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG AAG
Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys
30 65 70 75 80

CAG CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG
Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
85
90
95

CGC ACC ATC TTC TTC AAG GAC GAC GGC AAC TAC AAG ACC CGC GCC GAG

Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu

100 105 110

40 GTG AAG TTC GAG GGC GAC ACC CTG GTG AAC CGC ATC GAG CTG AAG GGC

Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly

115 120 125

ATC GAC TTC AAG GAG GAC GGC AAC ATC CTG GGG CAC AAG CTG GAG TAC 432 45 Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr 130 135

AAC TAC AAC AGC CAC AAC GTC TAT ATC ATG GCC GAC AAG CAG AAG AAC 480 Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn 150 155 160

GGC ATC AAG GTG AAC TTC AAG ATC CGC CAC AAC ATC GAG GAC GGC AGC
Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser
165 170 175

GTG CAG CTC GCC GAC CAC TAC CAG CAG AAC ACC CCC ATC GGC GAC GGC

576

										242							
	Va	1 G	ln Le	eu A] 18	la As 30	p Hi	.в Ту	r Gl	n Gl 18	n As	n Th	ır Pı	ro Il	le Gl		sp Gly	
5	CC Pr	C GI o Va	TG CT		CG CC	C GA	C AA p As	C CA n Hi 20	в ту	C CI	G AG	GC AC	CC CA or Gl 20	n Se	C GO	CC CTG .a Leu	624
10	AG Se:	C AA r Ly 21		C CC p Pr	C AA	C GA n Gl	G AA u Ly 21	s ar	C GA g As	T CA p Hi	C AT s Me	G GI t Va 22	l Le	G CT u Le	G GA u Gl	G TTC u Phe	672
15	GT(Val 225		C GC r Al	C GC a Al	C GG a Gl	G AT y Ile 23	= In:	T CT	C GG u Gl	C AT y Me	G GA t As 23	p Gl	G CT u Le	G TA u Ty	C AA r Ly	G TCC s Ser 240	720
	GG# Gly	A CTO	C AG. u Ar	A TC	T CG r Arg 245	ANTO	r caz a Glr	A GC	T TC	C ATO	t Se	C GA r Gl	G AC	G GT(C AT 1 11 25	C ATG e Met 5	768
20	AGC Ser	GA(G ACC	G GT(r Val 260		TGT Cys	TCC Ser	C AGO	C CGC Arg 265	J Ala	C AC	T GTO	G ATO	G CTT Let 270	и Ту:	T GAT	816
25	GAT Asp	Gly Gly	2 AA0 / Asr 275	LLys	G CGA G Arg	TGG Trp	CTC Leu	CCT Pro	Ala	GGC Gly	C ACC	G GGT	r ccc / Pro 285	Glr	GC0 Ala	C TTC	864
30	AGC Ser	CGC Arg 290		CAC Gln	ATC	TAC Tyr	CAC His 295	AAC Asn	CCC Pro	ACG Thr	GCC Ala	AAT Asn 300	Ser	TTT	CGC Arg	GTC Val	912
35	GTG Val 305	GGC	CGG Arg	AAG Lys	ATG Met	CAG Gln 310	CCC Pro	GAC Asp	CAG Gln	CAG Gln	GTG Val 315	Val	ATC	AAC Asn	TG1 Cys	GCC Ala 320	960
	ATC Ile	GTC Val	CGG Arg	GGT Gly	GTC Val 325	AAG Lys	TAT Tyr	AAC Asn	CAG Gln	GCC Ala 330	ACC Thr	CCC	AAC Asn	TTC Phe	CAT His	CAG Gln	1008
40	TGG Trp	CGC Arg	GAC Asp	GCT Ala 340	CGC Arg	CAG Gln	GTC Val	TGG Trp	GGC Gly 345	CTC Leu	AAC Asn	TTC Phe	GGC Gly	AGC Ser 350	AAG Lys	GAG Glu	1056
45	GAT Asp	GCG Ala	GCC Ala 355	CAG Gln	TTT Phe	GCC Ala	GCC Ala	GGC Gly 360	ATG Met	GCC Ala	AGT Ser	GCC Ala	CTA Leu 365	GAG Glu	GCG Ala	TTG Leu	1104
50	GAA Glu	GGA Gly 370	GGT Gly	GGG Gly	CCC Pro	FIU	CCA Pro 375	CCC Pro	CCA Pro	GCA Ala	CTT Leu	CCC Pro 380	ACC Thr	TGG Trp	TCG Ser	GTC Val	1152
55	CCG / Pro / 385	AAC Asn	GGC Gly	CCC Pro	JCI	CCG Pro 390	GAG Glu	GAG Glu	GTG Val	GAG Glu	CAG Gln 395	CAG Gln	AAA Lys	AGG Arg	CAG Gln	CAG Gln 400	1200
	CCC	3GC	CCG	TCG	GAG	CAC .	ATA	GAG	CGC	CGG	GTC	TCC	AAT	GCA	GGA	GGC	1248 242

										270							
	Pro	Gly	Pro	Ser	Glu 405	His	Ile	Glu	Arg	Arg 410	Val	Ser	Asn	Ala	Gly 415	Gly	
5						GCT Ala											1296
10						CCC Pro											1344
15						GGA Gly											1392
13						GGC Gly 470											1440
20						GCT Ala										_	1488
25						GGG Gly											1536
30						CTC Leu											1584
35			Lys			CAA Gln									_		1632
33						CCA Pro 550											1680
40						GAG Glu											1728
45						ACC Thr											1776
50						GAC Asp										_	1824
e e						TTG Leu											1872
55	TTC	GTC	CAG	GAG	CTG	AGG	AAG	CGG	GGT	TCT	ccc	TGA					1908 2 4

244

Phe Val Gln Glu Leu Arg Lys Arg Gly Ser Pro 625 630 635

5 (2) INFORMATION FOR SEQ ID NO:125:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 635 amino acids
 - (B) TYPE: amino acid
- (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (v) FRAGMENT TYPE: internal

15

10

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:125:

	Τ.		. Ser		5					10					15	
20			Leu	20					25					3.0	Ser	
			Glu 35					40					45			
25		50	Thr				55					60				
	65		Tyr			70					75					B O
			Asp		85					90					95	
30			Ile	100					105					110		
			Phe 115					120					125			
35		130	Phe				135					140				
	145		Asn			150					155					160
			Lys		165					170					175	Ser
40			Leu	180					185					190		
			Leu 195					200					205			
45		210	Asp				215					220	Leu			
	445		Ala			230					235					240
	Gly	Leu	Arg	Ser	Arg 245	Ala	Gln	Ala	Ser	Met 250	Ser	Glu	Thr	Val	Ile 255	Met
50	Ser	Glu	Thr	Val 260	Ile	Cys	Ser	Ser	Arg 265	Ala	Thr	Val	Met	Leu 270	Tyr	Asp
			Asn 275					280					285	Gln		
5 5		290	Val				295					300	Ser			
	Val	Gly	Arg	Lys	Met	Gln	Pro	Asp	Gln	Gln	Val	Val	Ile	Asn	Cys	Ala

245

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310
                                       315
     Ile Val Arg Gly Val Lys Tyr Asn Gln Ala Thr Pro Asn Phe His Gln
                 325
                                  330
     Trp Arg Asp Ala Arg Gln Val Trp Gly Leu Asn Phe Gly Ser Lys Glu
5
                               345
     Asp Ala Ala Gln Phe Ala Ala Gly Met Ala Ser Ala Leu Glu Ala Leu
                  360
                                    365
     Glu Gly Gly Pro Pro Pro Pro Ala Leu Pro Thr Trp Ser Val
                        375
                                          380
10
     Pro Asn Gly Pro Ser Pro Glu Glu Val Glu Gln Gln Lys Arg Gln Gln
                     390
                                       395
     Pro Gly Pro Ser Glu His Ile Glu Arg Arg Val Ser Asn Ala Gly Gly
                  405
                         410
     Pro Pro Ala Pro Pro Ala Gly Gly Pro Pro Pro Pro Pro Gly Pro Pro
15
            420
                               425
     Pro Pro Pro Gly Pro Pro Pro Pro Gly Leu Pro Pro Ser Gly Val
                                    445
                  440
     Pro Ala Ala His Gly Ala Gly Gly Pro Pro Pro Ala Pro Pro
20
     Leu Pro Ala Ala Gln Gly Pro Gly Gly Gly Ala Gly Ala Pro Gly
                    470
                                       475
     Leu Ala Ala Ile Ala Gly Ala Lys Leu Arg Lys Val Ser Lys Gln
                                   490
     Glu Glu Ala Ser Gly Gly Pro Thr Ala Pro Lys Ala Glu Ser Gly Arg
25
              500
                               505
     Ser Gly Gly Gly Leu Met Glu Glu Met Asn Ala Met Leu Ala Arg
                             520
                                             525
     Arg Arg Lys Ala Thr Gln Val Gly Glu Lys Thr Pro Lys Asp Glu Ser
                        535
                                           540
30
     Ala Asn Gln Glu Pro Glu Ala Arg Val Pro Ala Gln Ser Glu Ser
            550
                                     555
     Val Arg Arg Pro Trp Glu Lys Asn Ser Thr Thr Leu Pro Arg Met Lys
                                  570
                  565
     Ser Ser Ser Ser Val Thr Thr Ser Glu Thr Gln Pro Cys Thr Pro Ser
35
        580 585 590
     Ser Ser Asp Tyr Ser Asp Leu Gln Arg Val Lys Gln Glu Leu Leu Glu
                             600
     Glu Val Lys Lys Glu Leu Gln Lys Val Lys Glu Glu Ile Ile Glu Ala
       610 615
40
     Phe Val Gln Glu Leu Arg Lys Arg Gly Ser Pro
             (2) INFORMATION FOR SEQ ID NO:126:
```

45 (i) SEQUENCE CHARACTERISTICS:

(ix) FEATURE:

50

55

- (A) LENGTH: 1329 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

- (A) NAME/KEY: Coding Sequence
- (B) LOCATION: 1...1326
 - (D) OTHER INFORMATION:

246

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:126:

5	ATO Met	G GT	G AG l Se	C AAG	G GGG G Gly 5	C GAC	GAC Glu	TCTC	TTC	C ACC E Thi	C GGG	G GT y Va	G GT	G CC	C ATO	C CTG e Leu	48
10	GT(Va]	C GAG	G CTO u Leo	G GAG u Ası 20	GGG Gly	C GAC / Asp	GTA Val	AAC Asr	GG(Gl ₃ 25	C CAC	C AAC	TTO	C AGO	C GTC Val	TC	C GGC r Gly	96
15	GIU	GI	35	и стУ	Asp) Ala	Thr	Tyr 40	Gly	' Lys	Leu	ı Thi	45	Lys	Phe	C ATC	144
	TGC Cys	ACC Thi	C ACC	GGC Gly	AAG Lys	CTG Leu	CCC Pro 55	GTG Val	Pro	TGG Trp	CCC Pro	ACC Thr	CTC	GTG Val	ACC Thr	ACC Thr	192
20	CTG Leu 65	ACC Thr	TAC	Gly	GTG Val	CAG Gln 70	TGC Cys	TTC Phe	AGC Ser	CGC Arg	TAC Tyr 75	CCC Pro	GAC Asp	CAC His	ATG Met	AAG Lys 80	240
2 5	CAG Gln	CAC	GAC Asp	TTC Phe	TTC Phe 85	AAG Lys	TCC Ser	GCC Ala	ATG Met	CCC Pro 90	GAA Glu	GGC Gly	TAC	GTC Val	CAG Gln 95	GAG Glu	288
30	CGC Arg	ACC Thr	ATC Ile	TTC Phe 100	TTC Phe	AAG Lys	GAC Asp	GAC Asp	GGC Gly 105	AAC Asn	TAC Tyr	AAG Lys	ACC Thr	CGC Arg 110	GCC Ala	GAG Glu	336
35	GTG Val	AAG Lys	TTC Phe 115	GAG Glu	GGC Gly	GAC Asp	ACC Thr	CTG Leu 120	GTG Val	AAC Asn	CGC Arg	ATC Ile	GAG Glu 125	CTG Leu	AAG Lys	GGC Gly	384
	ATC Ile	GAC Asp 130	TTC Phe	AAG Lys	GAG Glu	GAC Asp	GGC Gly 135	AAC Asn	ATC Ile	CTG Leu	GGG Gly	CAC His 140	AAG Lys	CTG Leu	GAG Glu	TAC Tyr	432
40	AAC Asn 145	TAC Tyr	AAC Asn	AGC Ser	CAC His	AAC Asn 150	GTC Val	TAT Tyr	ATC Ile	ATG Met	GCC Ala 155	GAC Asp	AAG Lys	CAG Gln	AAG Lys	AAC Asn 160	480
45	GGC Gly	ATC Ile	AAG Lys	GTG Val	AAC Asn 165	TTC Phe	AAG Lys	ATC Ile	CGC Arg	CAC His 170	AAC Asn	ATC Ile	GAG Glu	GAC Asp	GGC Gly 175	AGC Ser	528
50	GTG Val	CAG Gln	CTC Leu	GCC Ala 180	GAC Asp	CAC His	TAC (Gln	CAG Gln 185	AAC Asn	ACC Thr	CCC Pro	ATC Ile	GGC Gly 190	GAC Asp	GGC Gly	576
55	CCC Pro	GTG Val	CTG Leu 195	CTG Leu	CCC Pro	GAC Asp	Asn 1	CAC His	TAC Tyr	CTG Leu	AGC Ser	Thr	CAG Gln 205	TCC Ser	GCC Ala	CTG Leu	624
	AGC .	AAA	GAC	CCC .	AAC (GAG 1	AAG (CGC (GAT	CAC .	ATG (GTC	CTG	CTG	GAG	TTC	672 24 6

SUBSTITUTE SHEET (RULE 26)

	Ser		Asp	Pro	Asn	Glu		Arg	Asp	His	Met	Val 220	Leu	Leu	Glu	Phe	
						ATC						GAG					720
5	Val 225	Thr	Ala	Ala	Gly	11e 230	Thr	Leu	GIA	Met	235	Glu	Leu	Tyr	гÀв	240	
10						GCT Ala											768
				Val	GGT	GAT Asp			Cys	GGA				Leu		_	816
15	~=~			260	~~~	a. a	mm o	003	265	ama	mam	oma.	ccc	270	CTC.	mmr.	864
						CAG Gln											804
20						GAT Asp								_	_		912
25						GCT Ala 310										_	960
30						ACC Thr											1008
25						GAA Glu											1056
35						AAC Asn											1104
40						GAG Glu											1152
45						CCT Pro 390											1200
50						ATG Met											1248
						ATG Met											1296
55	GGG	AAG	AAA	AAA	TCT	GGT	TGC	CTT	GTC	TTG	TGA						1329 247

248

Gly Lys Lys Lys Ser Gly Cys Leu Val Leu 435 440

```
5 (2) INFORMATION FOR SEQ ID NO:127:
```

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 442 amino acids
 - (B) TYPE: amino acid
- 10 (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
 - (ii) MOLECULE TYPE: protein
 - (v) FRAGMENT TYPE: internal
- 15
 - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:127:

	1			Lys	5					10					15	
20				Asp 20					25					3.0	Ser	
			35	Gly				40					45			
25		50		Gly			55					60				
	65			Gly		70					75					RΛ
	Gln	His	Asp	Phe	Phe 85	Lys	Ser	Ala	Met	Pro	Glu	Gly	Tyr	Val	Gln	Glu

- 30 Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
 100 105 110
 - Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
 115 120 125
- Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr

 135 130 135 140
- 165 170 175

 40 Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
- val Gin Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
 180 185 190
 Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu
- 195 200 205
 Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe
- 45 210 215 220
 Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser
 - 225 230 235 240
 Gly Leu Arg Ser Arg Ala Gln Ala Ser Met Ala Ala Ile Arg Lys Lys
- 50 Leu Val Ile Val Gly Asp Gly Ala Cys Gly Lys Thr Cys Leu Leu Ile
 - Val Phe Ser Lys Asp Gln Phe Pro Glu Val Tyr Val Pro Thr Val Phe
 275 280 285
- Glu Asn Tyr Val Ala Asp Ile Glu Val Asp Gly Lys Gln Val Glu Leu
 290 295 300
 Ala Leu Trp Asp Thr Ala Gly Gln Glu Asp Tyr Asp Arg Leu Arg Pro

	305					310					315					320		
	Leu	Ser	Tyr	Pro	Asp 325	Thr	Asp	Val	Ile	Leu 330	Met	Cys	Phe	Ser	Ile 335	Asp		
5	Ser	Pro	Asp	Ser 340	Leu	Glu	Asn	Ile	Pro 345	Glu	Lys	Trp	Thr	Pro 350	Glu	Val		
-	Lys	His	Phe 355		Pro	Asn	Val	Pro 360		Ile	Leu	Val	Gly 365		Lys	Lys		
	Asp	Leu 370		Asn	Asp	Glu	His		Arg	Arg	Glu	Leu 380		Lys	Met	Lys		
10			Pro	Val	Lys			Glu	Gly	Arg		Met	Ala	Asn	Arg	Ile 400		
	385 Glv	Δla	Phe	Glv	Tyr	390 Met	Glu	Cvs	Ser	Δla	395 Lvs	Thr	Lvs	Asn	Glv	_		
	-			-	405			-		410	-	Leu	_	_	415			
15	Arg	Giu	vai	420	Gru	Mec	MIG	1111	425	Ата	ATG	neu	GIII	430	ALG	Arg		
	Gly	Lys	Lys 435	Lys	Ser	Gly	Сув	Leu 440	Val	Leu								
			(2)	INI	FORM	ATIO	v FOI	R SEQ	O ID	NO:	128:							
20		(-	; \	COLLEG	JCE (CHARA	A CTE	ייים ד	rce.									
		(-		_		1140												
						ucle												
25						ONESS Y: 1:		_	3									
20			(2)	101		• • •		•										
			ii) N ix) N			TYP	E: cI	DNA										
30			(7)		4E / 121	ev. (rodi.	C.	~									
30						EY: (ON: 1		_	edne	ice								
			(D)	OTI	HER :	INFO	RMAT	ON:										
		(2	xi) S	SEQUI	ENCE	DESC	CRIP:	rion	: SE	Q ID	NO:	128:						
35		~~~	G 3 M	m. m	G 3 M	mam	ar a	G			~ m	m> 0	200	ar a	CON	G N N	4	0
												TAC Tyr				_	4	0
	1	•		,	5					10	-	-			15			
40	GAG	GAC	TGG	GAC	CGG	GAC	CTG	CTC	CTG	GAC	CCG	GCC	TGG	GAG	AAG	CAG	9	6
	Glu	Asp	Trp	_	Arg	Asp	Leu	Leu		Asp	Pro	Ala	Trp		Lys	Gln		
				20					25					30				
	CAG	AGA	AAG	ACA	TTC	ACG	GCA	TGG	TGT	AAC	TCC	CAC	CTC	CGG	AAG	GCG	14	4
45	Gln	Arg	Lys 35	Thr	Phe	Thr	Ala	Trp	Cys	Asn	Ser	His	Leu 45	Arg	Lys	Ala		
			33					40					45					
												CGG					19	2
50	Gly	Thr 50	Gln	lle	Glu	Asn	11e 55	Glu	Glu	Asp	Phe	Arg 60	Asp	GIA	Leu	Lys		
		- •										- 0						
												CGC					24	0
	Leu 65	мес	Leu	ьеи	ьeu	70	vaı	тте	ser	GIY	G1u 75	Arg	ьeu	АТА	ràs	Pro 80		
55						. =												
	GAG	CGA	GGC	AAG	ATG	AGA	GTG	CAC	AAG	ATC	TCC	AAC	GTC	AAC	AAG	GCC	28	
																		24

										250							
	G1	u A	rg G	ly Ly	/s Me 85	t Ar	g Va	al Hi	s Ly	s Il 90	e Se	r As	n Va	l As	n Ly 95	rs Ala	ı
5				10	0	a 56	т пу	s GI	y va 10	1 L y 5	s Lei	u Va	l Se	r Il 11	e Gl O	A GCC y Ala	
10			11	.5	ı Aş	p GI	y AS.	12	0 т гу	s Me	t Thi	r Lei	125	/ Me	t Il	C TGG e Trp	
15		13	0	- 20	u AI	a vr	13!	p Pro 5	o Pro	o Va.	L Ala	140	Met	: Va	l Se	C AAG r Lys	432
	145	5		. . .	u File	150	. 61)	y val	l Va.	l Pro	155	Leu	val	Glı	ı Lei	G GAC 1 Asp 160	480
20	-3	1	, va.	. ASI	165	nis	. rys	s Pne	e Ser	170	Ser	Gly	Glu	Gly	Gli 175		528
25	GAT Asp	GCC Ala	ACC Thi	TAC Tyr 180	. Ory	AAG Lys	CTG Leu	ACC Thr	CTG Leu 185	Lys	TTC Phe	ATC Ile	TGC Cys	ACC Thr 190	ACC Thr	GGC Gly	576
30	AAG Lys	CTG Leu	CCC Pro 195	• • • • •	CCC Pro	TGG Trp	CCC Pro	ACC Thr 200	CTC Leu	GTG Val	ACC Thr	ACC Thr	CTG Leu 205	ACC Thr	TAC	GGC	624
35		210	, -	1110	AGC Ser	AIG	215	Pro	Asp	His	Met	Lys 220	Gln	His	Asp	Phe	672
	TTC Phe 225	AAG Lys	TCC Ser	GCC Ala	ATG Met	CCC Pro 230	GAA Glu	GGC Gly	TAC Tyr	GTC Val	CAG Gln 235	GAG Glu	CGC Arg	ACC Thr	ATC Ile	TTC Phe 240	720
40	TTC Phe	AAG Lys	GAC Asp	GAC Asp	GGC Gly 245	AAC Asn	TAC Tyr	AAG Lys	ACC Thr	CGC Arg 250	GCC Ala	GAG Glu	GTG Val	AAG Lys	TTC Phe 255	GAG Glu	768
45	GGC Gly	GAC Asp	ACC Thr	CTG Leu 260	GTG Val	AAC Asn	CGC Arg	TIE	GAG Glu 265	CTG Leu	AAG (GGC Gly	Ile	GAC Asp 270	TTC Phe	AAG Lys	816
50	GAG (GAC Asp	GGC Gly 275	AAC Asn	ATC Ile	CTG Leu	GIY	CAC His 280	AAG Lys	CTG Leu	GAG 1	Tyr I	AAC : Asn :	FAC Fyr	AAC Asn	AGC Ser	864
55	CAC A	AAC Asn 290	GTC Val	TAT Tyr	ATC .	met 1	GCC Ala 295	GAC /	AAG Lys	CAG A	Lys A	AAC (Asn (GGC #	ATC .	AAG Lys	GTG Val	912
	AAC 1	rtc .	AAG	ATC	CGC (CAC 1	AAC i	ATC (GAG (GAC (GC A	AGC C	GTG C	AG (CTC	gcc	960 250

										251							
	Asn 305	Phe	Lys	Ile	Arg	His 310	Asn	Ile	Glu	Asp	Gly 315	Ser	Val	Gln	Leu	Ala 320	
5											GAC Asp						1008
10											GCC Ala						1056
15											GAG Glu			-			1104
15						ATG Met					AAG Lys	TAA					1140
20			(2)	IN)	FORM	ATIO	v FOI	R SEC	מו כ	NO:	129:						
25		(:	i) SI (A) (B) (C)	EQUEI LENG TYPI STRI	NCE (GTH: E: ar	CHARA 379 mino ONESS	ACTEI amin acio	RIST: no ao i ingle	ICS:								
30		(7	/) FI	RAGMI	ENT :	TYPI TYPE	int	terna	al) ID	NO . 1	120.					
35	Met 1									-	NO:		Met	Gln	Pro 15	Glu	
		Asp	Trp	Asp 20	Arg	Asp	Leu	Leu	Leu 25		Pro	Ala	Trp	Glu 30		Gln	
	Gln	Arg	Lys 35	Thr	Phe	Thr	Ala	Trp 40	Cys	Asn	Ser	His	Leu 45	Arg	Lys	Ala	
40	-	50					55			-	Phe	60	-	_		_	
	65					70				_	Glu 75 Ser	_			_	80	
45		_	_	-	85	_			-	90	Leu				95		
				100					105		Thr			110			
50		Ile	115				Asp	120			Ala	Thr	125				
	Gly 145	130 Glu	Glu	Leu	Phe	Thr 150	135 Gly	Val	Val	Pro	Ile 155	140 Leu	Val	Glu	Leu	Asp 160	
55		Asp	Val	Asn	Gly 165		Lys	Phe	Ser	Val 170	Ser	Gly	Glu	Gly	Glu 175		
	Asp	Ala	Thr	Tyr	Gly	Lys	Leu	Thr	Leu		Phe	Ile	Cys	Thr	Thr	Gly	0.5

				180					185	i				190			
								201	2				205	Thr	Tyr	Gly	
5		Gln 210					213					222	Gln	His			
						200					235	Glu				~	
		Lys			273					250	Ala	Glu					
10		Asp		200					265	Leu	Lys			~~~			
		Asp						_ / N I	Lys	Leu			205				
15		Asn 290					233					200	Gly				
		Phe										Ser					
	Asp	His	Tyr	Gln	Gln 325	Asn	Thr	Pro	Ile	Gly 330	Asp	Gly	Pro	Val		320 Leu	
20	Pro	Asp	Asn	His 340		Leu	Ser	Thr	Gln 345	Ser	Ala	Leu	Ser		335 Asp	Pro	
	Asn	Glu	Lys 355	Arg	Asp	His	Met	Val 360	Leu	Leu	Glu			350 Thr	Ala	Ala	
25	Gly	Ile 370	Thr	Leu	Gly		Asp 375	Glu	Leu	Tyr	Lys		365				
			(2)	INF	ORMA			er.) ID	NO 7	2.0						
		(i) SE							NO: T	30:						
30			(A) : (B) '	LENG	TH:	3516	bas	е ра	irs								
			(C) 1 (D) 7	STRA	NDED	NESS	: si	ngle									
35			i) Mo														
		(i)	c) FE	EATUI	RE:		CDI	W.A.									
			(A) (B)	NAME	E/KEY	ζ: Co √: 1.	ding	g Se	quen	ce							
40			(D)	отн	ER IN	FORM	IATIC	ON:									
		(xi) SE	QUEN	ICE I	ESCR	IPTI	ON:	SEQ	ID N	JO:13	30:					
45	ATG C Met V	TG A	GC A	AG G	GC G	AG G	AG C	TG	TTC A	ACC G	GG G	TG G	TG C	CC A	TC C	TG	48
	1				5		14 1	eu i	1	.nr (età A	al V	al P		le L 5	eu	
	GTC G	AG C	TG G	AC G	GC G	AC G	TA A	AC C	GC C	AC A	AG I	TC A	GC G	TG T	CC G	GC	96
50	Val G		2	0	-y A	sp v	ат А	sn (15 15	lıs L	ys P	he S	er V 3		er G	ly	
	GAG G	GC G	AG G	GC G	AT G	CC A	CC T	AC G	GC A	AG C	TG A	CC C'	TG A	AG T	TC A	TC	144
55	Glu G	3!	- u	y A	~P A	10 T	nr T	yr G	ту Г	ys L	eu T	hr Lo	eu L	ys P	he I	le	
	TGC A	CC A	CC G	GC A	AG C	TG C	CC G	TG C	сс т	GG C	CC A	CC C	rc g	rg A	CC A	CC	192
																	252

										253							
	Сув	Thr 50	Thr	Gly	Lys	Leu	Pro 55	Val	Pro	Trp	Pro	Thr 60	Leu	Val	Thr	Thr	
5					GTG Val												240
10					TTC Phe 85												288
45					TTC Phe												336
15					GGC Gly												384
20					GAG Glu												432
25					CAC His												480
30					AAC Asn 165												528
					GAC Asp												576
35					CCC Pro												624
40					AAC Asn												672
45					GGG Gly												720
50					CGA Arg 245												768
					GCC Ala												816
55	GAG	CTT	GAC	TTC	TCC	ATC	CTC	TTC	GAC	ТАТ	GAG	TAT	TTG	AAT	CCG	AAC	864 2

	Gl	u Le	u As 27	p Ph 5	e Se	r Ile	e Le	u Ph 28	e As	254 р Ту		и Ту	r Le 28		n Pr	o Asn	
5	GA/ Gli	A GA 1 Gl 29	u 01	G CC u Pr	G AA O As:	T GCA	A CA' a His 295	з Гу	G GT(C GC	C AG a Se	C CC r Pr 30	o Pr	C TC	C GG r Gl	A CCC y Pro	912
10	GC# Ala 305	ту.	C CC	C GA' o As _l	r GA' P As _l	T GTA p Val 310	Met	GA(C TAT	r GGG	C CTO y Leu 319	ı Ly	G CCA	А ТАО Э Тул	C AG	C CCC r Pro 320	960
15	Бей	, AT	a 5e.	r net	325	r Gly	GIU	ı Pro) Pro	330	/ Arg	y Phe	e Gly	/ Glu	335		1008
	AIG	val	r GI)	340)	ıьуs	Phe	: Leu	345	Ala	ı Ala	Lys	Pro	350	Gly	G GCC / Ala	1056
20	Ser	Gly	355	ser	Pro	Arg	Ile	Glu 360	Ile	Thr	Pro	Ser	365	Glu	Leu	ATC Ile	1104
25	GIN	370	Val	. СІУ	Pro	ьeu	Arg 375	Met	Arg	Asp	Ala	Gly 380	Leu	Leu	Val	GAG Glu	1152
30	CAG Gln 385	Pro	CCC Pro	CTG Leu	GCC Ala	GGG Gly 390	GTG Val	GCC Ala	GCC Ala	AGC Ser	CCG Pro 395	AGG Arg	TTC Phe	ACC Thr	CTG Leu	CCC Pro 400	1200
35	GTG Val	CCC Pro	GGC Gly	TTC Phe	GAG Glu 405	GGC Gly	TAC Tyr	CGC Arg	GAG Glu	CCG Pro 410	CTT Leu	TGC Cys	TTG Leu	AGC Ser	CCC Pro 415	GCT Ala	1248
	AGC Ser	AGC Ser	GGC	TCC Ser 420	TCT Ser	GCC Ala	AGC Ser	TTC Phe	ATT Ile 425	TCT Ser	GAC Asp	ACC Thr	TTC Phe	TCC Ser 430	CCC Pro	TAC Tyr	1296
40	ACC Thr	TCG Ser	CCC Pro 435	TGC Cys	GTC Val	TCG Ser	CCC Pro	AAT Asn 440	AAC Asn	GGC Gly	GGG Gly	CCC Pro	GAC Asp 445	GAC Asp	CTG Leu	TGT Cys	1344
45	CCG Pro	CAG Gln 450	TTT Phe	CAA Gln	AAC Asn	ATC Ile	CCT Pro 455	GCT Ala	CAT His	TAT Tyr	TCC Ser	CCC Pro 460	AGA Arg	ACC Thr	TCG Ser	CCA Pro	1392
50	ATA Ile 465	ATG Met	TCA Ser	CCT Pro	CGA Arg	ACC Thr 470	AGC Ser	CTC Leu	GCC Ala	GAG Glu	GAC Asp 475	AGC Ser	TGC Cys	CTG Leu	GGC Gly	CGC Arg 480	1440
55	CAC His	TCG Ser	CCC Pro	GTG Val	CCC Pro 485	CGT Arg	CCG Pro	GCC Ala	TCC Ser	CGC Arg 490	TCC Ser	TCA Ser	TCG Ser	CCT Pro	GGT Gly 495	GCC Ala	1488
	AAG	CGG	AGG	CAT	TCG	TGC (GCC (GAG	GCC	TTG	GTT	GCC	CTG	CCG	ccc	GGA	1536 254

	Lys	Arg	Arg	His 500	Ser	Cys	Ala	Glu		Leu	Val	Ala	Leu	Pro 510	Pro	Gly		
5		TCA Ser															1584	
10		GCA Ala 530															1632	
45		TCT Ser															1680	
15		TGT Cys	_	_													1728	
20		GTG Val															1776	
25		GCC Ala															1824	
30		GCT Ala 610															1872	
		GTG Val															1920	
35		CCA Pro															1968	
40		ATC Ile															2016	
45		GGC Gly															2064	
50		CAG Gln 690															2112	
		ATT Ile															2160	
55	CAG	GTG	CAC	CGA	ATC	ACG	GGG	AAA	ACT	GTC	ACC	ACC	ACC	AGC	TAT	GAG	2208	255

										256							
	Glr	ı Va	l His	s Arg	725	Thi	c Gly	/ Lys	Thr	730		Thi	Thi	r Sei	735	Glu S	
E	AAG	ATA	A GTO	GGC	AAC	ACC	: AAA	GTC	CTG	GAG	ATC	ccc	TTC	GAG	ccc	: AAA	2256
5	гÀа	: 116	e Val	740	/ Asr	ı Thr	Lys	val	. Leu 745		ılle	Pro	Let	750		Lys	
	AAC	AAC	ATO	AGG	GCA	ACC	ATC	GAC	TGT	GCG	GGG	ATC	TTC	AAC	CTI	AGA	2304
10			755	i				760					765	;		Arg	
	AAC	GCC	GAC	ATT	' GAG	CTG	CGG	AAA	GGC	GAG	ACG	GAC	ATI	GGA	AGA	AAG	2352
15	ASII	770	Asp	, 116	Glu	Leu	775		Gly	Glu	Thr	780		Gly	Arg	Lys	
	AAC	ACG	CGG	GTG	AGA	CTG	GTT	TTC	CGA	GTT	CAC	ATC	CCA	GAG	TCC	AGT	2400
	Asn 785	Thr	Arg	Val	Arg	Leu 790	Val	Phe	Arg	Val	His 795	Ile	Pro	Glu	Ser	Ser 800	
20	GGC	AGA	ATC	GTC	TCT	TTA	CAG	ACT	GCA	TCT	AAC	CCC	ATC	GAG	TGC	TCC	2448
	Gly	Arg	Ile	Val	Ser 805	Leu	Gln	Thr	Ala	Ser 810	Asn	Pro	Ile	Glu	Cys 815	Ser	
25	CAG	CGA	TCT	GCT	CAC	GAG	CTG	CCC	ATG	GTT	GAA	AGA	CAA	GAC	ACA	GAC	2496
25	GIn	Arg	Ser	Ala 820	His	Glu	Leu	Pro	Met 825	Val	Glu	Arg	Gln	Asp 830	Thr	Asp	
	AGC	TGC	CTG	GTC	TAT	GGC	GGC	CAG	CAA	ATG	ATC	CTC	ACG	GGG	CAG	AAC	2544
30	ser	Cys	ьеи 835	Val	Tyr	Gly	Gly	Gln 840	Gln	Met	Ile	Leu	Thr 845	Gly	Gln	Asn	
	TTT	ACA	TCC	GAG	TCC	AAA	GTT	GTG	TTT	ACT	GAG	AAG	ACC	ACA	GAT	GGA	2592
	FIIE	850	ser	GIU	ser	гуs	Val 855	Val	Phe	Thr	Glu	Lys 860	Thr	Thr	Asp	Gly	
35	GD G	~~~															
	Gln	Gln	Ile	TGG	GAG Glu	ATG Met	GAA Glu	GCC Ala	ACG	GTG Val	GAT	AAG	GAC	AAG	AGC	CAG	2640
	865			-		870	-			· u _	875	Dy S	Asp	цуъ	ser	880	
40	CCC	AAC	ATG	CTT	TTT	GTT	GAG	ATC	CCT	GAA	TAT	CGG	AAC	AAG	CAT	ATC	2688
	Pro	Asn	Met	Leu	Phe 885	Val	Glu	Ile	Pro	Glu	Tyr	Arg	Asn	Lys	His	Ile	
										890					895		
45	CGC	ACA Thr	CCT Pro	GTA Val	AAA	GTG Val	AAC Asn	TTC	TAC	GTC	ATC	AAT	GGG	AAG	AGA	AAA	2736
	,			900	-10	, 41	71511	FILE	905	vaı	ше	Asn	GIY	ւys 910	Arg	Lys	
	CGA	AGT	CAG	CCT	CAG	CAC	TTT	ACC	TAC	CAC	CCA	GTC	CCA	GCC	ΔTC	AAG	2784
50	Arg	Ser	Gin	Pro	Gln	His	Phe	Thr	Tyr	His	Pro	Val	Pro	Ala	Ile	Lys	2704
50			915					920					925				
	ACG	GAG	CCC	ACG	GAT	GAA	TAT	GAC	CCC	ACT	CTG	ATC	TGC	AGC	CCC	ACC	2832
	Thr	930	PLO	1111	Аѕр	GIU	Tyr 935	Asp	Pro	Thr		Ile 940	Cys	Ser	Pro	Thr	
55	ריאים י	CCZ	ccc	CTC	000	200											
	CAT	GGA	GGC	CIG	じじい	AGC	CAG	CCT	TAC	TAC	CCC	CAG	CAC	CCG	ATG	GTG	2880
																	256

	His 945	Gly	Gly	Leu	Gly	Ser 950	Gln	Pro	Tyr	Tyr	Pro 955	Gln	His	Pro	Met	Val 960	
5			TCC Ser														2928
10			ACG Thr														2976
15			GCC Ala 995				Gln					Leu					3024
13	Leu		TAT Tyr			Pro					Ala						3072
20			CAC His		Ser					Ala					Gln		3120
25			CTG Leu	Leu					Thr					Ser			3168
30			TAC Tyr					Gln					Gly				3216
		Phe	CAG Gln 1075				Tyr					Ala		_	_		3264
35	Arg		GGC Gly			Pro					Gln					_	3312
40			CCC Pro		Val					Asn					Arg		3360
45			AAC Asn	Gly					Asp					Leu			3408
50			ACC Thr					Gln					Thr				3456
EE		Val	AAT Asn 1155				Arg					Gly					3504
55	ААТ	CAG	ACG	TAA													3516 257

258

Asn Gln Thr 1170

45

210

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5
               (2) INFORMATION FOR SEQ ID NO:131:
            (i) SEQUENCE CHARACTERISTICS:
              (A) LENGTH: 1171 amino acids
              (B) TYPE: amino acid
10
             (C) STRANDEDNESS: single
             (D) TOPOLOGY: linear
            (ii) MOLECULE TYPE: protein
            (v) FRAGMENT TYPE: internal
15
            (xi) SEQUENCE DESCRIPTION: SEQ ID NO:131:
     Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu
                     5
                                        10
20
      Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
                                 25
     Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
                                40
     Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr
25
                            55
                                        60
     Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys
                        70
     Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
                                       90
30
     Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
                                   105
     Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
                               120
                                                  125
     Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr
35
                           135
                                               140
     Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn
                       150
                                 155
     Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser
                   165
                                      170
40
     Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
                                   185
                                                      190
     Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu
                     200
     Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe
```

Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser 230 235 Gly Leu Arg Ser Arg Ala Met Asn Ala Pro Glu Arg Gln Pro Gln Pro 245 250 50 Asp Gly Gly Asp Ala Pro Gly His Glu Pro Gly Gly Ser Pro Gln Asp 265 Glu Leu Asp Phe Ser Ile Leu Phe Asp Tyr Glu Tyr Leu Asn Pro Asn

215

275 280 285 Glu Glu Glu Pro Asn Ala His Lys Val Ala Ser Pro Pro Ser Gly Pro

55 295 300 Ala Tyr Pro Asp Asp Val Met Asp Tyr Gly Leu Lys Pro Tyr Ser Pro

175

5	Arg Ser Gln Gln 385 Val	Val Gly Ala 370 Pro	Gly Leu 355 Val	Pro 340 Ser	325 Gln Pro	Lys	Phe			330	_		_	Glu	335	_
	Arg Ser Gln Gln 385 Val	Val Gly Ala 370 Pro	Gly Leu 355 Val	Pro 340 Ser	325 Gln Pro	Lys	Phe			330	_		_		335	_
	Ser Gln Gln 385 Val Ser	Gly Ala 370 Pro	Leu 355 Val	340 Ser	Pro	-		Leu	Ser	Δla	Δla	T 110	_	_	_	
10	Gln Gln 385 Val Ser	Ala 370 Pro	355 Val			Arg			345		AIU	пув	Pro	Ala 350	Gly	Ala
10	Gln 385 Val Ser	370 Pro		Gly	Pro		He	Glu 360	Ile	Thr	Pro	Ser	His 365	Glu	Leu	Ile
10	385 Val Ser		Pro		110	Leu	Arg 375	Met	Arg	Asp	Ala	Gly 380	Leu	Leu	Val	Glu
	Ser	Pro		Leu	Ala	Gly 390	Val	Ala	Ala	Ser	Pro 395	Arg	Phe	Thr	Leu	Pro 400
			Gly	Phe	Glu 405	Gly	Tyr	Arg	Glu	Pro 410	Leu	Cys	Leu	Ser	Pro 415	Ala
15		Ser	Gly	Ser 420	Ser	Ala	Ser	Phe	Ile 425	Ser	Asp	Thr	Phe	Ser 430	Pro	Tyr
	Thr	Ser	Pro 435	Cys	Val	Ser	Pro	Asn 440	Asn	Gly	Gly	Pro	Asp 445	Asp	Leu	Cys
		450					455			_		460	_	Thr		
20	465				_	470					475		-	Leu	_	480
					485	_				490				Pro	495	
25	_	_	_	500		-			505					Pro 510		-
			515					520					525	Ser		
30		530			_		535				_	540		Pro		
30	545					550	_				555			Thr	_	560
		_	_		565		_		_	570				His	575	
35				580				-	585	_			_	590 Arg		_
			595				-	600	•			_	605	Pro	_	
40		610					615					620	-	Ala	_	
	625					630		=			635			Tyr		640
					645					650		-		Tyr	655	
45				660					665		_			670 His		
	Val	Gln	675 Leu	His	Gly	Tyr	Met	680 Glu	Asn	Lys	Pro	Leu	685 Gly	Leu	Gln	Ile
50	Phe	690 Ile	Gly	Thr	Ala	Asp	695 Glu	Arg	Ile	Leu	Lys	700 Pro	His	Ala	Phe	Tyr
	705 Gln	Val	His	Arg		710 Thr	Gly	Lys	Thr	Val	715 Thr	Thr	Thr	Ser	Tyr	720 Glu
	Lys	Ile	Val	_	725 Asn	Thr	Lys	Val		730 Glu	Ile	Pro	Leu	Glu	735 Pro	Lys
55				740	λ Ι.	'The	Tlo	λαn	745	Ala	Glv	Ile	Leu	750 Lvs	Leu	Ara

260

				_												
	7.~~	7. 7	755					760)				765	5		
		,,,	,				775	,				700				Lys
5	,05					790					795	Ile	Pro			Ser
	Gly	Arg	Ile	Val	Ser 805	Leu	Gln	Thr	Ala	Ser 810	Asn	Pro	Ile	Glu		800 Ser
	Gln	Arg	Ser	Ala 820	His		Leu	Pro	Met	Val	Glu	Arg	Gln			Asp
10	Ser	Сув	Leu 835	Val	Tyr	Gly	Gly	Gln	825 Gln	Met	Ile	Leu	Thr	830 830	Gln	Asn
	Phe	Thr 850	Ser		Ser	Lys	Val	840 Val	Phe	Thr	Glu		845 Thr	Thr	Asp	Gly
15	Gln 865			Trp	Glu	Met	855 Glu	Ala	Thr	Val	Asp	860 Lys	Asp	Lys	Ser	Gln
.0	003				Phe	870					875					000
	Arg	Thr	Pro	Val	885 Lys	Val	Asn	Phe	Tyr	890 Val	Ile	Asn	Gly	Lys	895 Arg	Lys
20			Gln	200	Gln				905					910		
		Glu	212		Asp			920					925			
		230			Gly		935					940				
25	743					950					955					0.00
					Ser 965					970					975	
30				980	Leu				985					000		
00	Pro		223				1	.000				1	0.0E			
		010				T	015				1	020				
35	Asp .				1	030				1	035					040
	Ser .				045				1	050				7	Pro	Val
40	Ile		T	000				1	065				7	Ser	His	
40	Glu :		0/5				1	080				1	Pro	Gly		
		0 9 0				Τ,	095				7	Arg :	Leu			
45	Ser 7				1.	110				7	Ala '	Thr :				100
	Ala 1	Lys .	Asn (Gly 1	Pro 1 125	Pro '	Val :	Ser .	Asp 1	Gln . 130	Lys (3lu '	Val		Pro .	120 Ala
	Gly V	Val '	Thr :	Ile : 140	Lys (3ln (Glu (Gln ,	Asn 145	Leu .	Asp (3ln :		Tyr :	135 Leu <i>l</i>	Asp
50	Asp V	/al /			Ile I	le A	Arg 1	Lys (160	Glu :	Phe	Ser (Pro :	150 Pro <i>l</i>	Ala A	Arg
	Asn (•	- • •				1.	165			

55 (2) INFORMATION FOR SEQ ID NO:132:

261

5		()	(A) (B) (C) (D)	LENC TYPE STRA TOPO	ETH: E: nu ANDEI OLOGY CULE	CHARA 3546 iclei ONESS (: li	bas c ac s: si near	e pa id ngle	airs										
10			(B)	LO	CATIO	EY: C ON: 1 INFOR	3	543	equer	ıce									
15		AAC	GCC	ccc	GAG	CGG	CAG	ccc	CAA	ccc	GAC	GGC						48	
	met 1	Asn	Ala	Pro	5 5	Arg	GIN	Pro	GIN	10	Asp	GIA	GIY	Asp	15	PIO			
20						GGC Gly										_		96	
25						TAT Tyr											1	.44	
30						CCA Pro										_	1	.92	
35						AAG Lys 70										_	2	40	
						TTC Phe											2	88	
40						AAG Lys											3	36	
45						TCC Ser								_			3	884	
50						GGC Gly										GGG Gly		132	
55						AGG Arg 150	_										4	180	
55	TAC	CGC	GAG	CCG	CTT	TGC	TTG	AGC	CCC	GCT	AGC	AGC	GGC	TCC	TCT	GCC	5	528	2

										262							
	Ту	r Ar	g Glu	ı Pro	Le:	ı Cys	5 Lei	ı Sei	r Pro	Ala 170		r Sei	Gly	/ Ser	Se:	r Ala	
5	AG(Sei	TTO Phe	C ATT	TCT Ser 180	Asp	C ACC	TTC Phe	TC(C CCC Pro 185	туг	C ACC	C TCC	CCC Pro	TGC Cys	Va]	C TCG l Ser	576
10	Pro	AAT Asr	AAC Asn 195	і Сіў	Gly	G CCC	GAC Asp	GAC Asp 200	Leu	TGT Cys	CCC Pro	G CAG	TTT Phe 205	Gln	AAC Asr	ATC lle	624
15	CCT Pro	GCT Ala 210	nış	TAT Tyr	TCC Ser	CCC Pro	AGA Arg 215	Thr	TCG Ser	CCA Pro	ATA Ile	ATG Met 220	TCA Ser	CCT Pro	CGA Arg	ACC Thr	672
	AGC Ser 225	Deu	GCC Ala	GAG Glu	GAC Asp	AGC Ser 230	TGC Cys	CTG Leu	GGC Gly	CGC Arg	CAC His 235	Ser	CCC Pro	GTG Val	CCC Pro	CGT Arg 240	720
20	CCG Pro	GCC Ala	TCC Ser	CGC Arg	TCC Ser 245	Ser	TCG Ser	CCT Pro	GGT Gly	GCC Ala 250	AAG Lys	CGG Arg	AGG Arg	CAT His	TCG Ser 255	TGC Cys	768
25	GCC Ala	GAG Glu	GCC Ala	TTG Leu 260	GTT Val	GCC Ala	CTG Leu	CCG Pro	CCC Pro 265	GGA Gly	GCC Ala	TCA Ser	CCC Pro	CAG Gln 270	CGC Arg	TCC Ser	816
30	CGG Arg	AGC Ser	CCC Pro 275	TCG Ser	CCG Pro	CAG Gln	CCC Pro	TCA Ser 280	TCT Ser	CAC His	GTG Val	GCA Ala	CCC Pro 285	CAG Gln	GAC Asp	CAC His	864
35	GGC Gly	TCC Ser 290	CCG Pro	GCT Ala	GGG Gly	TAC Tyr	CCC Pro 295	CCT Pro	GTG Val	GCT Ala	GGC Gly	TCT Ser 300	GCC Ala	GTG Val	ATC Ile	ATG Met	912
	GAT Asp 305	GCC Ala	CTG Leu	AAC Asn	AGC Ser	CTC Leu 310	GCC Ala	ACG Thr	GAC Asp	TCG Ser	CCT Pro 315	TGT Cys	GGG Gly	ATC Ile	CCC Pro	CCC Pro 320	960
40	AAG Lys	ATG Met	TGG Trp	AAG Lys	ACC Thr 325	AGC Ser	CCT Pro	GAC Asp	CCC Pro	TCG Ser 330	CCG Pro	GTG Val	TCT Ser	GCC Ala	GCC Ala 335	CCA Pro	1008
45	TCC Ser	AAG Lys	GCC Ala	GGC Gly 340	CTG Leu	CCT Pro	CGC Arg	CAC His	ATC Ile 345	TAC Tyr	CCG Pro	GCC Ala	Val	GAG Glu 350	TTC Phe	CTG Leu	1056
50	GGG Gly	CCC Pro	TGC Cys 355	GAG Glu	CAG Gln	GGC Gly	GLu	AGG Arg 360	AGA Arg	AAC Asn	TCG Ser	Ala	CCA Pro 365	GAA Glu	TCC Ser	ATC Ile	1104
55	CTG Leu	CTG Leu 370	GTT Val	CCG Pro	CCC Pro	Thr	TGG Trp 375	CCC Pro	AAG Lys	CCG Pro	Leu	GTG (Val :	CCT (GCC . Ala	ATT Ile	CCC Pro	1152
	ATC	TGC	AGC .	ATC (CCA	GTG :	ACT (GCA	TCC	CTC (CCT	CCA (CTT (GAG '	rgg	CCG	1200 2 6

										263							
	Ile 385	Cys	Ser	Ile	Pro	Val 390	Thr	Ala	Ser	Leu	Pro 395	Pro	Leu	Glu	Trp	Pro 400	
5					TCA Ser 405												1248
10					CGG Arg												1296
15					ACT Thr												1344
					CCT Pro												1392
20					AAG Lys												1440
25					ACC Thr 485												1488
30					ATC Ile												1536
35					GGG Gly												1584
33					ACG Thr												1632
40	_	_		_	CAC His	_											1680
45					AAC Asn 565												1728
50					GAA Glu												1776
55					ATC Ile												1824
	GTT	GTG	TTT	ACT	GAG	AAG	ACC	ACA	GAT	GGA	CAG	CAA	ATT	TGG	GAG	ATG	1872 2

										264					•		
	Va	1 Va 6:	al P) 10	ne Tì	ır G]	u Ly	's Th 61	r Th	r As	p Gl	y Gl:	n Gli 620		e Tr	p Gl	u Met	
5	62	5	.u 11	11 V C	II AS	63 ъ гу	S As O	р гу	s Se	r Gl	n Pro 635	Asr 5	n Met	: Le	ı Ph	T GTT e Val 640	1920
10	-		.C 11	.0 91	64	F AF	g As:	n Ly	s Hi	5 Ile 650	e Arg	g Thr	Pro	Va]	65!		1968
15			,	66	0	C AS.	ir Gr	у гу	669	J Lys	s Arg	, Ser	Gln	Pro 670	Gli	G CAC	2016
	TTT Phe	T AC	C TA r Ty 67		C CC. s Pro	A GTO	C CCA	A GC0 > Ala 680	3 TT6	C AAC Lys	ACG Thr	GAG Glu	CCC Pro 685	ACG Thr	GAT Asp	GAA Glu	2064
20	тат Туг	GA As 69	P	C AC	r Lei	3 ATO	C TGC € Cys 695	s Ser	C CCC	ACC Thr	CAT His	GGA Gly 700	GGC Gly	CTG Leu	GGG Gly	AGC Ser	2112
25	CAG Gln 705		Г ТАС Э Туз	С ТАС г Туз	C CCC	CAC Glr 710	HIS	CCG Pro	ATG Met	GTG Val	GCC Ala 715	GAG Glu	TCC Ser	CCC Pro	TCC Ser	TGC Cys 720	2160
30	CTC Leu	GT(GCC L Ala	ACC Thr	725	ATA	CCC Pro	TGC Cys	CAG Gln	CAG Gln 730	TTC Phe	CGC Arg	ACG Thr	GGG Gly	CTC Leu 735	TCA Ser	2208
35	TCC Ser	CCT	GAC Asp	GCC Ala 740	Arg	TAC	CAG Gln	CAA Gln	CAG Gln 745	AAC Asn	CCA Pro	GCG Ala	Ala	GTA Val 750	CTC Leu	TAC Tyr	2256
	CAG Gln	CGG	AGC Ser 755	пåв	AGC Ser	CTG Leu	AGC Ser	CCC Pro 760	AGC Ser	CTG Leu	CTG Leu	GGC Gly	TAT Tyr 765	CAG Gln	CAG Gln	CCG Pro	2304
40	GCC Ala	CTC Leu 770	1100	GCC Ala	GCC Ala	CCG Pro	CTG Leu 775	TCC Ser	CTT Leu	GCG Ala	Asp	GCT Ala 1 780	CAC His	CGC Arg	TCT Ser	GTG Val	2352
45	CTG Leu 785	GTG Val	CAC His	GCC Ala	GGC Gly	TCC Ser 790	CAG Gln	GGC Gly	CAG Gln	Ser	TCA Ser 795	GCC (Ala 1	CTG (Leu]	CTC Leu :	CAC His	CCC Pro 800	2400
50	TCT Ser	CCG Pro	ACC Thr	AAC Asn	CAG Gln 805	CAG Gln	GCC Ala	TCG Ser	CCT Pro	GTG Val 810	ATC (CAC 1	FAC :	Ser 1	CCC Pro 815	ACC Thr	2448
55	AAC Asn	CAG Gln	CAG Gln	CTG Leu 820	CGC Arg	TGC Cys	GGA Gly	Ser	CAC His 825	CAG (Gln (GAG : Glu I	TTC C	3ln H	CAC A Nis 1	ATC . Ile 1	ATG Met	2496
	TAC	TGC	GAG	AAT	TTC	GCA	CCA	GGC .	ACC .	ACC I	AGA (CCT G	GC C	cg c	CCC (CCG	2544 26 4

										200							
	туг	Cys	Glu 835	Asn	Phe	Ala	Pro	Gly 840	Thr	Thr	Arg	Pro	Gly 845	Pro	Pro	Pro	
	GTC	AGT	CAA	GGT	CAG	AGG	CTG	AGC	CCG	GGT	TCC	TAC	CCC	ACA	GTC	ידע	2592
5		Ser															2332
		850		_		_	855			2		860					
	CAG	CAG	CAG	AAT	GCC	ACG	AGC	CAA	AGA	GCC	GCC	AAA	AAC	GGA	CCC	CCG	2640
		Gln	Gln	Asn	Ala		Ser	Gln	Arg	Ala	Ala	Lys	Asn	Gly	Pro	Pro	
10	865					870					875					880	
		AGT				-											2688
	Val	Ser	Asp	GIII	885	GIU	vai	ьец	PIO	890	GIĀ	vaı	Thr	тте	ьув 895	Gin	
15					003					050					093		
	GAG	CAG	AAC	TTG	GAC	CAG	ACC	TAC	TTG	GAT	GAT	GTT	AAT	GAA	ATT	ATC	2736
	Glu	Gln	Asn	Leu	Asp	Gln	Thr	Tyr	Leu	Asp	Asp	Val	Asn	Glu	Ile	Ile	
				900					905					910			
20		AAG															2784
	Arg	Lys		Phe	Ser	Gly	Pro		Ala	Arg	Asn	Gln		Arg	Ile	Leu	
			915					920					925				
	CAG	TCG	ACG	GTA	CCG	CGG	GCC	CGG	GAT	CCA	CCG	GTC	GCC	ACC	ATG	GTG	2832
25		Ser															
		930					935		_			940					
	AGC	AAG	GGC	GAG	GAG	CTG	TTC	ACC	GGG	GTG	GTG	CCC	ATC	CTG	GTC	GAG	2880
		Lys	Gly	Glu	Glu	Leu	Phe	Thr	Gly	Val	Val	Pro	Ile	Leu	Val	Glu	
30	945					950					955					960	
	CTG	GAC	GGC	GAC	GTA	AAC	GGC	CAC	AAG	TTC	AGC	GTG	TCC	GGC	GAG	GGC	2928
		Asp	_														
					965				_	970				_	975	_	
35																	
		GGC															2976
	GIU	Gly	Asp	980	1111	ıyı	GLY	rys	985	inr	Leu	гув	Pne	990 11e	Cys	Thr	
40	ACC.	ccc	א א מי	CTC	ccc	cmc	ccc	maa	000	3.00	ama.	ama	100	200	ama	200	2024
40		GGC Gly															3024
		01	995			•		1000	110	****	LCu		1005	1111	DCu	1111	
	TAC	GGC	GTG	CAG	TGC	TTC	AGC	CGC	TAC	CCC	GAC	CAC	ATG	AAG	CAG	CAC	3072
45		Gly	Val	Gln	Cys			Arg	Tyr	Pro	-		Met	Lys	Gln	His	
	1	1010]	1015					1020					
	GAC	TTC	TTC	AAG	TCC	GCC	ATG	ccc	GAA	GGC	TAC	GTC	CAG	GAG	CGC	ACC	3120
		Phe															
50	1025				1	1030					1035				:	L040	
	איזיכי	TTC	ጥጥር	באם	GAC	GAC	GGC	מממ	ጥ ል ር	ΔAG	ACC	CGC	GCC	GNG.	GTC.	AAC	3160
		Phe															3168
					1045		1			1050		3			1055	-,-	
55															-		
	TTC	GAG	GGC	GAC	ACC	CTG	GTG	AAC	CGC	ATC	GAG	CTG	AAG	GGC	ATC	GAC	3216
																	26

	266	
	Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly Ile Asp 1060 1065 1070	
5	TTC AAG GAG GAC GGC AAC ATC CTG GGG CAC AAG CTG GAG TAC AAC TAC Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr Asn Tyr 1075 1080 1085	3264
10	AAC AGC CAC AAC GTC TAT ATC ATG GCC GAC AAG CAG AAG AAC GGC ATC Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn Gly Ile 1090 1095 1100	3312
15	AAG GTG AAC TTC AAG ATC CGC CAC AAC ATC GAG GAC GGC AGC GTG CAG Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser Val Gln 1105 1110 1115 1120	3360
	CTC GCC GAC CAC TAC CAG CAG AAC ACC CCC ATC GGC GAC GGC CCC GTG Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly Pro Val 1125 1130 1135	3408
20	CTG CTG CCC GAC AAC CAC TAC CTG AGC ACC CAG TCC GCC CTG AGC AAA Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu Ser Lys 1140 1145 1150	3456
25	GAC CCC AAC GAG AAG CGC GAT CAC ATG GTC CTG CTG GAG TTC GTG ACC Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe Val Thr 1155 1160 1165	3504
30	GCC GCC GGG ATC ACT CTC GGC ATG GAC GAG CTG TAC AAG TAA Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys 1170 1175 1180	3546
35	(2) INFORMATION FOR SEQ ID NO:133: (i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 1181 amino acids (B) TYPE: amino acid (C) STRANDEDNESS: single	
40	(D) TOPOLOGY: linear (ii) MOLECULE TYPE: protein (v) FRAGMENT TYPE: internal	
45	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:133:	
	Met Asn Ala Pro Glu Arg Gln Pro Gln Pro Asp Gly Gly Asp Ala Pro 1 5 10 15 Gly His Glu Pro Gly Gly Ser Pro Gln Asp Glu Leu Asp Phe Ser Ile	
50	Leu Phe Asp Tyr Glu Tyr Leu Asn Pro Asn Glu Glu Glu Pro Asn Ala	
55	His Lys Val Ala Ser Pro Pro Ser Gly Pro Ala Tyr Pro Asp Asp Val 50 55 60 Met Asp Tyr Gly Leu Lys Pro Tyr Ser Pro Leu Ala Ser Leu Ser Gly 65	
00	Glu Pro Pro Gly Arg Phe Gly Glu Pro Asp Arg Val Gly Pro Gln Lys	

					85					90					95	
	Phe	Leu	Ser	Ala 100		ГÀЗ	Pro	Ala	Gly 105		Ser	Gly	Leu	Ser 110		Arg
5			115					120					125	Gly		
		130					135					140		Leu		
	145					150					155			Phe		160
10					165					170				Ser	175	
				180					185					Cys 190		
15			195					200					205	Gln -		
		210					215					220		Pro		
20	225					230					235			Val		240
20					245					250				His Gln	255	
				260					265					270 Gln		
25			275					280					285	Val		
		290					295					300		Ile		
30	305					310			_		315	-	-	Ala		320
					325					330				Glu	335	
				340					345					350 Glu		
35			355					360					365	Ala		
		370					375					380		Glu		
40	385					390					395			Val		400
					405					410				Arg	415	
				420					425					430 His		
45			435					440					445	Thr		
		450					455					460		Arg		
50	465					470					475			Gly		480
					485					490				Arg	495	
	Ile	Asp		500 Ala	Gly	Ile	Leu	Lys	505 Leu	Arg	Asn	Ala	Asp	510 Ile	Glu	Leu
55	Arg	Lys	515 Gly	Glu	Thr	Asp	Ile	520 Gly	Arg	Lys	Asn	Thr	525 Arg	Val	Arg	Leu

													268								
			530						535	5					-	40					
	V	al	Phe	Arg	g Va	1 H	is I	le	Pro	G]	u s	er	Ser	r G]	ly A	ra	Ile	• Va	1 8	er	Leu
	G.	45 In	Th~	. 1 ת			5	50						55	55	,					560
5	0.	111	TIIL	AI	a se	r A	sn P 65	ro	Ile	G1	u C	ys	Ser	: G]	n A	rg	Ser	Al	ан	is	560 Glu
																					Gly
					58	0		-9 '	3111	AS	P 1	nr 85	Asp	Se	r C	ys	Leu	Va	1 T	yr	Gly
	G]	ly (Gln	Glr	Me	t I	le L	eu :	Chr	Gl	уG	ln	Asn	ı Ph	е т	hr :	car	59 	0		T
10																					
10	Vä	11 Y	val	Phe	Th:	r G]	u L	ys 1	hr	Th	r A	sp	Gly	Gl	n G	ln :	Ile	Tr	p G.	lυ	Met
	62	25			· .	· As	p L	75 F 30	sp	ьу	s S	er	Gln	Pr	O As	in N	1et	Le	u Pł	ıe	Val
	Gl	.u]	le	Pro	Glı	а Ту	r Ai	g A	sn	Lv	s H	is	Tle	63	5 ~ თ.⊁	T	٠	 .			640
15																					
	As	n F	he	Tyr	Va]	l Il	e As	n G	ly	Lys	s Aı	g	Lys	Ar	g Se	ro	ln	Pro	co GD c	n	Hic
	Ph	ет	'n'n	Тъл-	660) . D					66	55						670)	•••	*****
			***	675	nıs	PE	o Va	II P	ro	Ala	l]	e	Lys	Th	r Gl	u P	ro	Thi	: As	p	Glu
20							u Il														
	Gli	n P	ro	Tyr	Tyr	Pr	o Gl	n H	is	Pro	Me	t '	Val	Ala	ı Gl	u S	er	Pro		r 1	7220
25	Det	u v	aı.	AIA	Thr	72!	t Al	a P	ro	Cys	Gl	n (Gln	Phe	Ar	g T	hr	Gly	Le	u s	Ser
							у Ту														
	Glr	1 A:	rg s	Ser	Lys	Sei	Le	u Se	er	Pro	Se	- r 1	Leu	Leu	Gly	∕ Τγ	7 7	750 Gln	G),	. r	ro
30																					
	71.20	72	5u 1	ie c	Ala	Ala	Pro	o Le	eu :	Ser	Le	u A	Ala .	Asp	Ala	a Hi	is .	Arg	Sei	r v	al
							Sei														
35	Ser	Pr	o I	hr.	Asn	Gln	Glr	ı Al	a s	Ser	Pro	οV	al :	Ile	His	Tv	r s	Ser	Pro	יט ידי	00 hr
33																					
	*****	. 01	.11 (111	ьец 820	Arg	Cys	G1	у	Ser	His	G	ln (Glu	Phe	Gl	n I	His	Ile	М	et
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40																					
40	Val	Se	r G	ln (Gly	Gln	Arg	Le	u S	er	Pro	G	ly s	Ser	Tvr	84 Pr	c or	'hr	Wal	Τ.	1.0
	Gln	85 G1:	0 n c	1 m 1				85	5				•		860		-		vai	1.	re
	Gln 865	G1.	11 G	111 £	Asn	Ala	Thr 870	Se	r G	ln	Arg	A.	la A	lla	Lys	As	n G	lу	Pro	Pı	ro
	Val	Se	r A	sp (Iln	Lvs	Glu	Va	1 T.		Dwa	Α.	8	375				_		88	30
45																					
	Glu	Gl	n A	sn I	eu .	Asp	Gln	Thi	T	yr	Leu	As	sp A	ga	Val	Ası	n G	1,,	895	т 1	
	Arg	пу	s G. 9:	LUL # 15	ne :	Ser	Gly	Pro	P.	ro.	Ala	Aı	g A	sn	Gln	Thi	c A	rg	Ile	Le	u
50																					
	Gln																				
	Ser 945	Lys	G]	yс	lu (3lu	Leu	Phe	T	hr (Gly	Va	1 V	al	940 Pro	Tle	ь т	e1, 1	(/a)	C1	
55	Leu	ns [, Gl	у А	sp (/al 965	Asn	Gly	H	is)	Lys	Ph	e S	er '	Val	Ser	G.	ly (3lu	Gl	У
	Glu																				
		•		_		-	.,-	-ry	۲٠,	, a l	JCU	T.U	E Lie	eu 1	ьуs	Phe	: I.	le (Cys	Th	r

	980 985 990	
	Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr Leu Thr 995 1000 1005	
5	Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys Gln His 1010 1015 1020	
J	Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu Arg Thr	
	025 1030 1035 1040 Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu Val Lys	
	1045 1050 1055	
10	Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly Ile Asp 1060 1065 1070	
	Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr Asn Tyr	
	1075 1080 1085 Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn Gly Ile	
15	1090 1095 1100	
	Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser Val Gln 105 1110 1115 1120	
	Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly Pro Val	
20	1125 1130 1135 Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu Ser Lys	
	1140 1145 1150	
	Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe Val Thr 1155 1160 1165	
	Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys	
25	1170 1175 1180	
	(2) INFORMATION FOR SEQ ID NO:134:	
	(i) SEQUENCE CHARACTERISTICS:	
30	(A) LENGTH: 2802 base pairs	
	(B) TYPE: nucleic acid (C) STRANDEDNESS: single	
	(D) TOPOLOGY: linear	
35	(ii) MOLECULE TYPE: cDNA	
	(ix) FEATURE:	
	(A) NAME/KEY: Coding Sequence	
	(B) LOCATION: 12799	
40	(D) OTHER INFORMATION:	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:134:	
	ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG	3
45	Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu 1 5 10 15	
	1 5 10 15	
	GTC GAG CTG GAC GGC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly	5
50	20 25 30	
	GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC 144	1
•	Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile	
55	35 40 45	
•	TGC ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC	2
		269

	_									2/0							
	Cy	5 Th	r Th	r Gl	у Lу	s Le	u Pr 55	o Va	l Pr	o Tr	p Pr	O Th		u Va	l Th	r Thr	
5	CTO Let 65	3 AC 1 Th	C TA r Ty	C GG r Gl	С GT y Va	G CA6 1 Gli 70	G TG	C TT s Ph	C AG e Se	C CG	C TA g Ty 75	C CC r Pr	C GA	C CA p Hi	C AT	G AAG t Lys 80	240
10	CAC Glr	CA:	C GA	C TT	C TTO e Pho 85	C AAG e Lys	G TC	C GCC	C ATO	G CCC Pro	C GA	A GG u Gl	С ТАО у Ту:	C GT	C CA(1 Gl) 95	G GAG n Glu	288
15	CGC Arg	: AC	C ATO	C TTO Pho 100	= Pne	C AAC E Lys	GAC Asp	C GAO	C GG(p Gl _y 105	/ Asr	С ТАО 1 Туз	C AAG	G ACC	C CGC Arg	g Ala	C GAG a Glu	336
	GTG Val	Lys	F TTC F Phe 115	- 010	G GGC	C GAC / Asp	ACC Thr	Leu 120	val	AAC Asr	CGC Arg	C ATO	C GAC ∈ Glu 125	Let	AAC Lys	G GGC	384
20	ATC Ile	GAC Asp 130	PILE	Lys	GAG Glu	GAC Asp	GGC Gly 135	Asn	ATC	CTG	GGG Gly	CAC His	Lys	CTC Leu	GAG Glu	TAC Tyr	432
25	AAC Asn 145	TAC	AAC Asn	: AGC	CAC His	AAC Asn 150	GTC Val	TAT Tyr	T ATC	ATG Met	GCC Ala 155	Asp	AAG Lys	CAG Gln	AAG Lys	AAC Asn 160	480
30	GGC Gly	ATC Ile	AAG Lys	GTG Val	AAC Asn 165	TTC Phe	AAG Lys	ATC Ile	CGC Arg	CAC His 170	AAC Asn	ATC	GAG Glu	GAC Asp	GGC Gly 175	AGC Ser	528
35	GTG Val	CAG Gln	CTC Leu	GCC Ala 180	GAC Asp	CAC His	TAC Tyr	CAG Gln	CAG Gln 185	AAC Asn	ACC Thr	CCC Pro	ATC Ile	GGC Gly 190	GAC Asp	GGC Gly	576
	CCC Pro	GTG Val	CTG Leu 195	CTG Leu	CCC Pro	GAC Asp	AAC Asn	CAC His 200	TAC Tyr	CTG Leu	AGC Ser	ACC Thr	CAG Gln 205	TCC Ser	GCC Ala	CTG Leu	624
40		AAA Lys 210	GAC Asp	CCC Pro	AAC Asn	GAG Glu	AAG Lys 215	CGC Arg	GAT Asp	CAC His	ATG Met	GTC Val 220	CTG Leu	CTG Leu	GAG Glu	TTC Phe	672
45	GTG Val 225	ACC Thr	GCC Ala	GCC Ala	GGG Gly	ATC Ile 230	ACT Thr	CTC Leu	GGC Gly	ATG Met	GAC Asp 235	GAG Glu	CTG Leu	TAC Tyr	AAG Lys	TCC Ser 240	720
50	GGA Gly	CTC Leu	AGA Arg	TCT Ser	CGA Arg 245	GGG Gly	AGC Ser	ATG Met	Gly	ACC Thr 250	TTG Leu	CGG Arg	GAT Asp	TTA Leu	CAG Gln 255	TAC Tyr	768
55	GCG (CTC Leu	CAG Gln	GAG Glu 260	AAG Lys	ATC	GAG Glu	GIu	CTG Leu 265	AGG Arg	CAG Gln	CGG Arg	Asp	GCT Ala 270	CTC Leu	ATC Ile	816
	GAC (GAG	CTG	GAG	CTG (GAG '	TTG (GAT	CAG .	AAG (GAC	GAA	CTG	ATC	CAG	AAG	864 270

										211							
	Asp	Glu	Leu 275	Glu	Leu	Glu	Leu	Asp 280	Gln	Lys	Asp	Glu	Leu 285	Ile	Gln	Lys	
5		CAG Gln 290															912
10		CAG Gln															960
		AAG Lys															1008
15		CTC Leu															1056
20		GAT Asp															1104
25		GAG Glu 370															1152
30		TAT Tyr															1200
		GTG Val															1248
35		AAG Lys												_		_	1296
40		CTT Leu									_				_		1344
45		AAA Lys 450															1392
50		ACA Thr															1440
e-E		CCA Pro															1488
55	GAT	GTC	CTT	GAA	GAG	ACC	CAC	TAT	GAA	TĀA	GGA	GAA	TAT	ATT	ATC	AGG	1536 2

										272							
	As	p Va	al Le	eu G] 50	u Gl	u Th	r Hi	в Ту	r Gl 50	u As: 5	n Gl	y Gl	и Ту	r Il		e Arg	
5	CA G1	A GO	GT GO Ly Al 51	.u AI	A GG g Gl	G GA	C AC p Th	C TT r Ph 52	e Ph	T ATO	C ATO	C AGO	C AAA C Lys 525	Gl	A AC y Th	G GTA r Val	1584
10	115	53	0	IL AL	g GI	u As)	53!	r Pro 5	o Se	r Gli	ı Asp	540	Val	. Phe	e Le	T AGA u Arg	1632
15	545	5	u Gi	у пу	s GI	7 ASI 550))) Phe	e Gly	/ Glu	1 Lys 555	Ala	Leu	Glr	Gly	G GAA y Glu 560	1680
	,,,,,	, va	I AL	g 111.	565	a Asn	ı vaj	l Ile	≥ Ala	1 Ala 570	Glu	Ala	Val	Thr	Cys 575		1728
20	, ,		c na	580) ASL	ser	Pne	: гув	His 585	Leu	Ile	Gly	Gly	Leu 590	Asp	GAT Asp	1776
25	GTT Val	TC' Se	T AAT T ASI 595	Luy	A GCA 6 Ala	TAT	GAA Glu	GAT Asp 600	Ala	GAA Glu	GCT Ala	AAA Lys	GCA Ala 605	AAA Lys	TA1 Tyr	GAA Glu	1824
30	GCT Ala	GAZ Glu 610		G GCT Ala	TTC Phe	TTC Phe	GCC Ala 615	AAC Asn	CTG Leu	AAG Lys	CTG Leu	TCT Ser 620	GAT Asp	TTC Phe	AAC Asn	ATC	1872
35	ATT Ile 625	GAT Asp	ACC Thr	CTT Leu	GGA Gly	GTT Val 630	GGA Gly	GGT Gly	TTC Phe	GGA Gly	CGA Arg 635	GTA Val	GAA Glu	CTG Leu	GTC Val	CAG Gln 640	1920
	TTG Leu	AAA Lys	AGT Ser	GAA Glu	GAA Glu 645	TCC Ser	AAA Lys	ACG Thr	TTT Phe	GCA Ala 650	ATG Met	AAG Lys	ATT Ile	CTC Leu	AAG Lys 655	AAA Lys	1968
40	CGT Arg	CAC His	ATT	GTG Val 660	GAC Asp	ACA Thr	AGA Arg	CAG Gln	CAG Gln 665	GAG Glu	CAC His	ATC Ile	Arg	TCA Ser 670	GAG Glu	AAG Lys	2016
45	CAG Gln	ATC Ile	ATG Met 675	CAG Gln	GGG Gly	GCT Ala	CAT His	TCC Ser 680	GAT Asp	TTC Phe	ATA Ile	Val	AGA Arg 685	CTG Leu	TAC Tyr	AGA Arg	2064
50		TTT Phe 690	AAG Lys	GAC Asp	AGC Ser	пуѕ	TAT Tyr 695	TTG Leu	TAT Tyr	ATG Met	Leu l	ATG (Met (GAA (GCT Ala	TGT Cys	CTA Leu	2112
55	GGT Gly 705	GGA Gly	GAG Glu	CTC Leu	тър	ACC . Thr 710	ATT Ile	CTC Leu	AGG Arg	Asp .	AGA (Arg (GGT '	TCG ? Ser 1	TTT (GAA Glu	GAT Asp 720	2160
	TCT ;	ACA	ACC	AGA	TTT	TAC	ACA (GCA '	TGT (GTG (GTA (GAA (GCT T	TTT (GCC	TAT	2208 27 3

										2/3							
	Ser	Thr	Thr	Arg	Phe 725	Tyr	Thr	Ala	Cys	Val 730	Val	Glu	Ala	Phe	Ala 735	Tyr	
	CTG	СУТ	TCC	AAA	GGA	ATC	ביירע	ТΔС	AGG	GAC	CTC	אמ	CCA	GAA	ידממ	רידיר	2256
5				Lys													2230
Ū	Dea		501	740	O ₁	110	110	-7-	745	пър	Deu	ביום	110	750	non	LCu	
	ATC	CTA	GAT	CAC	CGA	GGT	TAT	GCC	AAA	CTG	GTT	GAT	TTT	GGC	TTT	GCA	2304
	Ile	Leu	Asp	His	Arg	Gly	Tyr	Ala	Lys	Leu	Val	qaA	Phe	Gly	Phe	Ala	
10			755					760					765				
	AAG	AAA	ATA	GGA	TTT	GGA	AAG	AAA	ACA	TGG	ACT	TTT	TGT	GGG	ACT	CCA	2352
	Lys	Lys	Ile	Gly	Phe	Gly	Lys	Lys	Thr	Trp	Thr	Phe	Cys	Gly	Thr	Pro	
		770					775					780					
15																	
	GAG	TAT	GTA	GCC	CCA	GAG	ATC	ATC	CTG	AAC	AAA	GGC	CAT	GAC	ATT	TCA	2400
	Glu	Tyr	Val	Ala	Pro	Glu	Ile	Ile	Leu	Asn	Lys	Gly	His	Asp	Ile	Ser	
	785					790					795					800	
20	GCC	GAC	TAC	TGG	TCA	CTG	GGA	ATC	CTA	ATG	TAT	GAA	CTC	CTG	ACT	GGC	2448
	Ala	Asp	Tyr	Trp	Ser	Leu	Gly	Ile	Leu	Met	Tyr	Glu	Leu	Leu	Thr	Gly	
					805					810					815		
	AGC	CCA	CCT	TTC	TCA	GGC	CCA	GAT	CCT	ATG	AAA	ACC	TAT	AAC	ATC	ATA	2496
25	Ser	Pro	Pro	Phe	Ser	Gly	Pro	Asp	Pro	Met	Lys	Thr	Tyr	Asn	Ile	Ile	
				820					825					830			
	TTG	AGG	GGG	ATT	GAC	ATG	ATA	GAA	TTT	CCA	AAG	AAG	ATT	GCC	AAA	AAT	2544
	Leu	Arg	Gly	Ile	Asp	Met	Ile	Glu	Phe	Pro	Lys	Lys	Ile	Ala	Lys	Asn	
30			835					840					845				
	_	_		TTA													2592
	Ala		Asn	Leu	Ile	Lys	_	Leu	Cys	Arg	Asp		Pro	Ser	Glu	Arg	
25		850					855					860					
35																	
				TTG													2640
		GIY	Asn	Leu	гÀв		GIY	vaı	гàг	Asp		GIn	ràs	HIS	rys	_	
	865					870					875					880	
40	Total	GAG	GGC	TTT	ממכ	TGG	CAA	GGC	מידים	ΔGΔ	מממ	GGT	ACC	ጥጥር	۵۵۵	CCT	2688
40				Phe													2000
	1 110	Olu	Ory	1110	885	115	Olu	Ory	БСи	890	цуз	Oly	1111	Deu	895	110	
					003					0,00					0,5,5		
	CCT	ATA	АТА	CCA	AGT	GTT	GCA	TCA	כככ	ACA	GAC	ACA	AGT	ААТ	ТТТ	GAC	2736
45				Pro													
				900					905					910			
	AGT	TTC	CCT	GAG	GAC	AAC	GAT	GAA	CCA	CCA	CCT	GAT	GAC	AAC	TCA	GGA	2784
				Glu													
50			915		•		•	920				•	925			•	
	TGG	GAT	ATA	GAC	TTC	TAA											2802
	Trp	Asp	Ile	Asp	Phe												
		930															
55																	

274

(2) INFORMATION FOR SEQ ID NO:135:

```
(i) SEQUENCE CHARACTERISTICS:
```

- (A) LENGTH: 933 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- 10 (v) FRAGMENT TYPE: internal

5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:135:

15					5					10					3 -	e Leu
				20					25	/ His				20	Sei	Gly
								40					45	Lys		lle
20		50					55					60				Thr
	0,5				' Val	70					75					0.0
25					Phe 85					90					0.5	Glu
				TOO					105					110	Ala	
			TTO		Gly			120					125	Leu	Lys	
30					Glu		135					740	Lys	Leu		
	143				His	120					155					160
35					Asn 165					170					175	Ser
				190	Asp				185					100	Asp	
40			193		Pro			200					205	Ser		
40		210			Asn		215					220	Leu			
						23 0					235					240
45					Arg 245					250					255	Tyr
				260	Lys				265					270	Leu	
50			2/5		Leu			280					285	Ile		
50		200			Leu		295					Ile	Arg			
	-05					3 1 0					215	Gln				220
55	Thr	Lys	Arg	Gln	Ala 325	Ile	Ser	Ala	Glu	Pro 330	Thr	Ala	Phe		Ile	Gln

Asp Leu Ser His Val Thr Leu Pro Phe Tyr Pro Lys Ser Pro Gln Ser

330 335

										2.0						
				340					345					350		
	Lys	Asp	Leu 355	Ile	Lys	Glu	Ala	Ile 360	Leu	Asp	Asn	Asp	Phe 365	Met	Lys	Asn
5	Leu	Glu 370	Leu	Ser	Gln	Ile	Gln 375	Glu	Ile	Val	Asp	Cys 380	Met	Tyr	Pro	Val
	Glu 385	Tyr	Gly	Lys	Asp	Ser 390	Cys	Ile	Ile	Lys	Glu 395	Gly	Asp	Val	Gly	Ser 400
		Val	Tyr	Val	Met 405		Asp	Gly	Lys	Val 410	Glu	Val	Thr	Lys	Glu 415	
10	Val	Lys	Leu	Cys 420	Thr	Met	Gly	Pro	Gly 425	Lys	Val	Phe	Gly	Glu 430	Leu	Ala
	Ile	Leu	Tyr 435	Asn	Cys	Thr	Arg	Thr 440	Ala	Thr	Val	Lys	Thr 445	Leu	Val	Asn
15	Val	Lys 450	Leu	Trp	Ala	Ile	Asp 455	Arg	Gln	Cys	Phe	Gln 460	Thr	Ile	Met	Met
	Arg 465	Thr	Gly	Leu	Ile	Lys 470	His	Thr	Glu	Tyr	Met 475	Glu	Phe	Leu	Lys	Ser 480
	Val	Pro	Thr	Phe	Gln 485	Ser	Leu	Pro	Glu	Glu 490	Ile	Leu	Ser	ГÀЗ	Leu 495	Ala
20	_			500				-	505		-		-	Ile 510		_
			515		_			520					525	Gly		
25		530					535					540		Phe		
	545					550					555			Gln		560
20					565					570				Thr	575	
30			-	580	-			-	585			_	_	Leu 590	_	
			595	-		-		600				_	605	Lys	-	
35		610					615			-		620	_	Phe Leu		
	625	_			_	630	_	_		•	635			Leu		640
40		_			645		-			650		-		Ser	655	_
40	_			660	_		_		665				_	670 Leu		
			675		-			680	-				685	Ala	-	_
45		690	_	_		_	695		_			700		Phe	_	
	705					710				_	715			Phe		720
50				_	725	-			-	730					735	Leu
				740				_	745	_		_		750 Gly		
			755		-		_	760	_			_	765	Gly		
55	Glu	770 Tyr	Val	Ala	Pro	Glu	775 Ile	Ile	Leu	Asn	Lys	780 Gly	His	Asp	Ile	Ser

	2/6	
	785 790 795 800	
	Ala Asp Tyr Trp Ser Leu Gly Ile Leu Met Tyr Glu Leu Leu Thr Gly	
5	Ser Pro Pro Phe Ser Gly Pro Asp Pro Met Lys Thr Tyr Asn Ile Ile	
	Leu Arg Gly Ile Asp Met Ile Glu Phe Pro Lys Lys Ile Ala Lys Asn	
	Ala Ala Asn Leu Ile Lys Lys Leu Cys Arg Asp Asn Pro Ser Glu Arg	
10	Leu Gly Asn Leu Lys Asn Gly Val Lys Asp Ile Gln Lys His Lys Trp	
	Phe Glu Gly Phe Asn Trp Glu Gly Leu Arg Lys Gly Thr Leu Thr Pro	
15	Pro Ile Ile Pro Ser Val Ala Ser Pro Thr Asp Thr Ser Asn Phe Asp	
	Ser Phe Pro Glu Asp Asn Asp Glu Pro Pro Pro Asp Asp Asn Ser Gly	
	Trp Asp Ile Asp Phe 925	
20	930	
	(2) INFORMATION FOR SEQ ID NO:136:	
25	(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 2799 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single	
	(D) TOPOLOGY: linear	
30	(ii) MOLECULE TYPE: cDNA (ix) FEATURE:	
35	(A) NAME/KEY: Coding Sequence(B) LOCATION: 12795(D) OTHER INFORMATION:	
00	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:136:	
	ATG GGC ACC TTG CGG GAT TTA CAG TAC GCG CTC CAG GAG AAG ATC GAG	48
40	Met Gly Thr Leu Arg Asp Leu Gln Tyr Ala Leu Gln Glu Lys Ile Glu 1 5 10 15	
	GAG CTG AGG CAG CGG GAT GCT CTC ATC GAC GAG CTG GAG CTG GAG TTG	96
45	Glu Leu Arg Gln Arg Asp Ala Leu Ile Asp Glu Leu Glu Leu Glu Leu 20 25 30	
40	GAT CAG AAG GAC GAA CTG ATC CAG AAG CTG CAG AAC GAG CTG GAC AAG	44
	Asp Gln Lys Asp Glu Leu Ile Gln Lys Leu Gln Asn Glu Leu Asp Lys 35 40 45	
50	TAC CGC TCG GTG ATC CGA CCA GCC ACC CAG CAG GCG CAG AAG CAG AGC	92
	Tyr Arg Ser Val Ile Arg Pro Ala Thr Gln Gln Ala Gln Lys Gln Ser 50 55 60	_
55	GCG AGC ACC TTG CAG GGC GAG CCG CGC ACC AAG CGG CAG GCG ATC TCC	40
00	Ala Ser Thr Leu Gln Gly Glu Pro Arg Thr Lys Arg Gln Ala Ile Ser 70 75 80	
		2.

5						GAT Asp 90					288
3 .						AAG Lys					336
10				_		TTG Leu			_	_	384
15	 	 			 	 GAG Glu	 				432
20						CTG Leu					480
25			_		_	GTG Val 170	_	_			528
						ATT Ile					576
30						GTA Val			_		624
35						AGG Arg					672
40						GTT Val					720
45	_					GAT Asp 250				_	768
		-				CAA Gln				_	816
50						AAT Asn					864
55						ACT Thr					912

		•															
5	TT' Pho 30:	6 61	SA GA y Gl	.G AA u Ly	A GCo s Ala	TTC a Leu 310	1 GI1	G GG(G GA	A GAT u Asp	r GTC Val	l Ar	A ACI	A GC	A AA a As	C GTA n Val 320	960
	AT'	F GC ≥ Al	T GC a Al	A GA a Gl	A GC: u Ala 325	a vai	ACC Thi	C TGC	CTT Let	T GTC 1 Val 330	Ile	GAC Asp	C AGA	A GAG	C TC	TTTT Phe	1008
10	AA/ Lys	A CA 5 Hi	T TT s Le	G AT' u Ile 340	a GTA	A GGG	Lev	GAT Asp	GAT Asp 345) Val	TCT Ser	'AA'	T AAA 1 Lys	GC/ Ala 350	туз	GAA Glu	1056
15	GAT Asp	GC.	A GAZ a Gli 35!	1 AIS	r AAA a Lys	GCA Ala	Lys	TAT Tyr 360	Glu	GCT Ala	GAA Glu	GCG	GCT Ala 365	Phe	TTC Phe	GCC Ala	1104
20	AAC Asn	Let 370	n riàs	G CTC	TCT Ser	GAT Asp	TTC Phe	AAC Asn	ATC	ATT Ile	GAT Asp	ACC Thr 380	Leu	GGA Gly	GTI Val	GGA Gly	1152
25	GGT Gly 385	PIIC	C GG# ∋ Gly	A CGA / Arg	GTA Val	GAA Glu 390	CTG Leu	GTC Val	CAG Gln	TTG Leu	AAA Lys 395	AGT Ser	GAA Glu	GAA Glu	TCC	AAA Lys 400	1200
	ACG Thr	TTT Phe	r GCA Ala	ATG Met	AAG Lys 405	ATT Ile	CTC Leu	AAG Lys	AAA Lys	CGT Arg 410	CAC His	ATT Ile	GTG Val	GAC Asp	ACA Thr 415	AGA Arg	1248
30	CAG Gln	CAG Gln	GAG Glu	CAC His 420	ATC Ile	CGC Arg	TCA Ser	GAG Glu	AAG Lys 425	CAG Gln	ATC Ile	ATG Met	CAG Gln	GGG Gly 430	GCT Ala	CAT His	1296
35	TCC Ser	GAT Asp	TTC Phe 435	ATA Ile	GTG Val	AGA Arg	CTG Leu	TAC Tyr 440	AGA Arg	ACA Thr	TTT Phe	AAG Lys	GAC Asp 445	AGC Ser	AAA Lys	TAT Tyr	1344
40	TTG Leu	TAT Tyr 450	Mec	TTG Leu	ATG Met	GAA Glu	GCT Ala 455	TGT Cys	CTA Leu	GGT Gly	GGA Gly	GAG Glu 460	CTC Leu	TGG Trp	ACC Thr	ATT Ile	1392
45	CTC Leu 465	AGG Arg	GAT Asp	AGA Arg	GGT Gly	TCG Ser 470	TTT Phe	GAA Glu	GAT Asp	Ser	ACA Thr 475	ACC Thr	AGA Arg	TTT Phe	TAC Tyr	ACA Thr 480	1440
	GCA Ala	TGT Cys	GTG Val	GTA Val	GAA Glu 485	GCT Ala	TT T Phe	GCC Ala	TAT Tyr	CTG Leu 490	CAT His	TCC Ser	AAA Lys	GGA Gly	ATC Ile 495	ATT Ile	1488
50	TAC Tyr	AGG Arg	GAC Asp	CTC Leu 500	AAG Lys	CCA (GAA Glu	Asn	CTC Leu 505	ATC	CTA (GAT Asp	His .	CGA Arg 510	GGT Gly	TAT Tyr	1536
55	GCC Ala	AAA Lys	CTG Leu 515	GTT Val	GAT (TTT (31A	TTT (Phe 2 520	GCA Ala	AAG /	AAA :	Ile	GGA ' Gly : 525	TTT Phe	GGA Gly	AAG Lys	1584

279

				TTT Phe							1632
5				GGC Gly							1680
10				GAA Glu 565							1728
15				ACC Thr							1776
20				AAG Lys							1824
25				AAT Asn							1872
				CAA Gln			_			_	1920
30				GGT Gly 645							1968
35				ACA Thr							2016
40				GAT Asp							2064
45		_	_	ACC Thr						_	2112
,,,				CTG Leu							2160
50				GGC Gly 725							2208
55				ATC Ile				 _			2256

280

5	AC(C CT	C GT u Va 75	T 111	C ACC	C CTC	G ACC	TAC Tyr 760	G13	C GTC	G CAG	TGC Cys	TTC Phe 765	Se	C CG	C TAC g Tyr	2304
	CCC Pro	GA(As)	o ur:	C ATO	G AAC	G CAG	CAC His 775	: Asp	TTC Phe	TTC Phe	: AAG : Lys	TCC Ser 780	Ala	ATC Met	G CC	C GAA	2352
10	GGC Gly 785	- 7 -	C GTC	C CAC	GAG Glu	CGC Arg 790	inr	: ATC	TTC Phe	TTC Phe	AAG Lys 795	GAC Asp	GAC Asp	GGC Gly	AA(Ası	TAC Tyr 800	2400
15	AAG Lys	Thi	C CGC	GCC Ala	GAG Glu 805	GTG Val	AAG Lys	TTC Phe	GAG Glu	GGC Gly 810	GAC Asp	ACC Thr	CTG Leu	GTG Val	AAC Asr	C CGC	2448
20	ATC Ile	GAG Glu	CTG Leu	Lys 820	GIA	ATC Ile	GAC Asp	TTC Phe	AAG Lys 825	GAG Glu	GAC Asp	GGC Gly	AAC Asn	ATC Ile 830	CTC Leu	GGG Gly	2496
25	CAC His	AAG Lys	CTG Leu 835	GAG Glu	TAC Tyr	AAC Asn	TAC Tyr	AAC Asn 840	AGC Ser	CAC His	AAC Asn	GTC Val	TAT Tyr 845	ATC Ile	ATG Met	GCC Ala	2544
	GAC Asp	AAG Lys 850	CAG Gln	AAG Lys	AAC Asn	GGC Gly	ATC Ile 855	AAG Lys	GTG Val	AAC Asn	TTC Phe	AAG Lys 860	ATC Ile	CGC Arg	CAC His	AAC Asn	2592
30	ATC Ile 865	GAG Glu	GAC Asp	GGC Gly	AGC Ser	GTG Val 870	CAG Gln	CTC Leu	GCC Ala	GAC Asp	CAC His 875	TAC Tyr	CAG Gln	CAG Gln	AAC Asn	ACC Thr 880	2640
35	CCC Pro	ATC Ile	GGC Gly	GAC Asp	GGC Gly 885	CCC Pro	GTG Val	CTG Leu	CTG Leu	CCC Pro 890	GAC Asp	AAC Asn	CAC His	TAC Tyr	CTG Leu 895	AGC Ser	2688
40	ACC Thr	CAG Gln	TCC Ser	GCC Ala 900	CTG Leu	AGC Ser	AAA Lys	Asp	CCC Pro 905	AAC Asn	GAG . Glu :	AAG Lys	Arg :	GAT Asp 910	CAC His	ATG Met	2736
45	GTC Val	CTG Leu	CTG Leu 915	GAG Glu	TTC Phe	GTG Val	Inr	GCC (Ala / 920	GCC Ala	GGG Gly	ATC :	Thr	CTC (Leu (925	GGC Gly	ATG Met	GAC Asp	2784
	GAG (TAA												2799
50			(2)	INF	ORMA'	rion	FOR	SEQ	ID 1	NO:1	37:						

- (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 932 amino acids
- (B) TYPE: amino acid

55

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:137:

Met Gly Thr Leu Arg Asp Leu Gln Tyr Ala Leu Gln Glu Lys Ile Glu Glu Leu Arg Gln Arg Asp Ala Leu Ile Asp Glu Leu Glu Leu Glu Leu Asp Gln Lys Asp Glu Leu Ile Gln Lys Leu Gln Asn Glu Leu Asp Lys Tyr Arg Ser Val Ile Arg Pro Ala Thr Gln Gln Ala Gln Lys Gln Ser Ala Ser Thr Leu Gln Gly Glu Pro Arg Thr Lys Arg Gln Ala Ile Ser Ala Glu Pro Thr Ala Phe Asp Ile Gln Asp Leu Ser His Val Thr Leu Pro Phe Tyr Pro Lys Ser Pro Gln Ser Lys Asp Leu Ile Lys Glu Ala Ile Leu Asp Asn Asp Phe Met Lys Asn Leu Glu Leu Ser Gln Ile Gln Glu Ile Val Asp Cys Met Tyr Pro Val Glu Tyr Gly Lys Asp Ser Cys Ile Ile Lys Glu Gly Asp Val Gly Ser Leu Val Tyr Val Met Glu Asp Gly Lys Val Glu Val Thr Lys Glu Gly Val Lys Leu Cys Thr Met Gly Pro Gly Lys Val Phe Gly Glu Leu Ala Ile Leu Tyr Asn Cys Thr Arg Thr Ala Thr Val Lys Thr Leu Val Asn Val Lys Leu Trp Ala Ile Asp Arg Gln Cys Phe Gln Thr Ile Met Met Arg Thr Gly Leu Ile Lys His Thr Glu Tyr Met Glu Phe Leu Lys Ser Val Pro Thr Phe Gln Ser Leu Pro Glu Glu Ile Leu Ser Lys Leu Ala Asp Val Leu Glu Glu Thr His Tyr Glu Asn Gly Glu Tyr Ile Ile Arg Gln Gly Ala Arg Gly Asp Thr Phe Phe Ile Ile Ser Lys Gly Thr Val Asn Val Thr Arg Glu Asp Ser Pro Ser Glu Asp Pro Val Phe Leu Arg Thr Leu Gly Lys Gly Asp Trp Phe Gly Glu Lys Ala Leu Gln Gly Glu Asp Val Arg Thr Ala Asn Val Ile Ala Ala Glu Ala Val Thr Cys Leu Val Ile Asp Arg Asp Ser Phe Lys His Leu Ile Gly Gly Leu Asp Asp Val Ser Asn Lys Ala Tyr Glu Asp Ala Glu Ala Lys Ala Lys Tyr Glu Ala Glu Ala Ala Phe Phe Ala Asn Leu Lys Leu Ser Asp Phe Asn Ile Ile Asp Thr Leu Gly Val Gly Gly Phe Gly Arg Val Glu Leu Val Gln Leu Lys Ser Glu Glu Ser Lys

										282	•					
	38					39	0				39	5				400
	Th	r Ph	e Al	a Me	t Lys 405	Il.	e Le	u Ly	s Ly	s Ar 41	g Hi	s Il	e Va	l As		400 r Arg
5	Glı	n Gl	n Gl	u Hi:	s Ile	Ar	g Se	r Gl	u Ly 42	s Gl	n Il	e Me	t Gl			5 a His
	Sei	r As	p Ph 43:	e Ile		Arg	g Le	и Ту 44	r Ar	g Th	r Ph	е Гу			o r Ly	s Tyr
	Let	1 Ty:	r Me		ı Met	Glu	ı Ala 45	а Су	s Le	1 G1	y Gl			5 u Trj) Th	r Ile
10	Leu 465	ı Arç	g As _l	p Arg	g Gly	Sei 470	Phe	e Gl	u Ası	Se:			o r Ar	g Phe	э Ту:	r Thr
	Ala	Суя	s Val	l Val	l Glu 485	Ala		⊇ Ala	а Туг	Let 490	475 4 His	s Sei	r Lys	s Gly		480 e Ile
15				200	ı Lys	Pro			508	ı Ile	e Let					y Tyr
	Ala	Lys	Let 515	ı Val	Asp	Phe	Gl _y	/ Phe	ala Ala	Lys	Lys	Ile			Gly	/ Lys
		330	,				535	Thr	Pro			540	١.	Pro		ılle
20						- ララレ						Туг	Trp			Gly 560
					505					570	Pro	Pro			625	Pro
25				200					585					FOO	Met	Ile
			223		Lys			600					COL	Ile		
30					Asn		012					C 2 A	Leu	Lys		
30					Gln	030					6 D E					
					Gly 645					650						
35				000	Thr				665					C70		
			0,5		Asp			h H ()					C D E			
40					Thr											
					Leu	/ T U					716					
					Gly 725					'73 N					72.5	
45	Thr			740	Ile o				745					750		
	Pro :		, ,,					760					700			
50	Gly 1						//3					700				
	785 Lys :															
	Ile (005					מוא					015	
55	His I			020					825					~ ~ ~		
													-1-		100	nta

•			835					840					B45					
	Asp	Lys 850	Gln	ГÀЗ	Asn	Gly	Ile 855	Lys	Val	Asn	Phe	860 Fàs	Ile	Arg	His	Asn		
	Ile	Glu	Asp	Gly	Ser	Val	Gln	Leu	Ala	Asp	His	Tyr	Gln	Gln	Asn	Thr		
5	865					870		_	_	_	875	_		_		880		
	Pro	Ile	GIA	Asp	885	Pro	Val	Leu	Leu	Pro 890	Asp	Asn	His	Tyr	Leu 895	Ser		
	Thr	Gln	Ser	Ala 900		Ser	Lys	Asp	Pro 905		Glu	Lys	Arg			Met		
10	Val	Leu			Phe	Val	Thr			Gly	Ile	Thr	Leu 925	910 Gly	Met	Asp		
	Glu	Leu	915 Tyr	Lys				920					923					
		930																
15			(2)	INI	FORM	ATION	1 FOI	R SE	O ID	NO: 1	138:							
		(:	i) sı	EQUE	ICE (CHARA	CTE	RIST	rcs:									
						2184			airs									
20									•									
			(D)	TOPO	OLOGY	Y: 1i	inea	r _										
		(:	ii) r	MOLE	CULE	TYPE	E: cl	ANC										
25		(:	ix)	FEAT	JRE:													
25	(B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: cDNA (ix) FEATURE: (A) NAME/KEY: Coding Sequence (B) LOCATION: 12181 (D) OTHER INFORMATION:																	
	(ii) MOLECULE TYPE: cDNA(ix) FEATURE:(A) NAME/KEY: Coding Sequence(B) LOCATION: 12181																	
	(ii) MOLECULE TYPE: cDNA(ix) FEATURE:(A) NAME/KEY: Coding Sequence(B) LOCATION: 12181																	
30		()	ci) s	SEQUI	ENCE	DESC	CRIP	rion	: SE	QI Ç	NO: 3	138:						
	λтα	GTG	NGC	אמכ	ccc	GAG	GNG	СТС	TTC	» CC	GGG	GTG	GTG	ccc	ልጥሮ	CTG	4.8	t
						Glu												
	1				5					10					15			
35	CTC	GNG	CTC	GNC	ccc	GAC	CT.	אאכי	ccc	CNC	אמכ	ጥጥር	አርር	стс	תככ	GGC	96	
						Asp										_	,	•
				20	_	_			25		_			30				
40	GAG	GGC	GAG	GGC	GAT	GCC	ACC	TAC	GGC	AAG	CTG	ACC	CTG	AAG	TTC	ATC	144	l .
	Glu	Gly	Glu	Gly	Asp	Ala	Thr	Tyr	Gly	Lys	Leu	Thr		Lys	Phe	Ile		
			35					40					45					
	TGC	ACC	ACC	GGC	AAG	CTG	CCC	GTG	CCC	TGG	ccc	ACC	CTC	GTG	ACC	ACC	192	2
45	Cys		Thr	Gly	ŗÀs	Leu		Val	Pro	Trp	Pro		Leu	Val	Thr	Thr		
		50					55					60						
•	CTG	ACC	TAC	GGC	GTG	CAG	TGC	TTC	AGC	CGC	TAC	CCC	GAC	CAC	ATG	AAG	240)
ာ 50		Thr	Tyr	Gly	Val	Gln	Cys	Phe	Ser	Arg	-	Pro	Asp	His	Met			
50	65					70					75					80		
						AAG										_	288	3
	Gln	His	Asp	Phe	Phe 85	Lys	Ser	Ala	Met	Pro 90	Glu	Gly	Tyr	Val	Gln 95	Glu		
55					03					J 0					د ر			
	CGC	ACC	ATC	TTC	TTC	AAG	GAC	GAC	GGC	AAC	TAC	AAG	ACC	CGC	GCC	GAG	336	5
																		2

										284							
	Ar	g Tì	hr I	le Ph 10	ne Ph	ie Ly	s As	p As	p Gl	y Ası 5	n Ty	r Lys	5 Thi	Ar 11		a Glu	
5	-		1:	15	u Gi	умь	p m	12(ı Va.)	L Asr	ı Ar	g Ile	125	Le	и Ьу	G GGC	384
10		13	0	с Бу	3 (1	u AS	135	y Asr	1 116	e Leu	ı Gly	His 140	Lys	Le	ı Gl	G TAC u Tyr	432
15	145	5	I AS	11 SC	ı nı	15(ı vaj	l Tyr	· Ile	: Met	155	Asp	Lys	Glr	1 Ьу	G AAC s Asn 160	480
	7		c by	s va	16	5	: ry	ile	Arg	His 170	Asn	lle	Glu	Asp	Gl ₂		528
20			20	180)	nis	lyr	GIN	G1n 185	Asn	Thr	Pro	Ile	Gly 190	Asp	GGC Gly	576
25			19!	5	· FIC	, wab	ASI	200	Tyr	Leu	Ser	Thr	Gln 205	Ser	Ala	CTG Leu	624
30		210)	, 110	ASI	GIU	11ys 215	Arg	Asp	His	Met	Val 220	Leu	Leu	Glu		672
35	225			ALG	GLY	230	inr	Leu	GIY	Met	Asp 235	GAG Glu	Leu	Tyr	Lys	Ser 240	720
	GGA Gly	CTC	AGA Arg	TCT Ser	CGA Arg 245	GGC Gly	ACC Thr	ATG Met	AGC Ser	GAC Asp 250	GTG Val	GCT . Ala	ATT Ile	GTG Val	AAG Lys 255	GAG Glu	768
40	1		БСи	260	гуз	Arg	GIY	Glu	Tyr 265	Ile	Lys	ACC !	Trp :	Arg 270	Pro	Arg	816
45	TAC Tyr	TTC Phe	CTC Leu 275	CTC Leu	AAG Lys	AAT Asn	Asp	GGC Gly 280	ACC Thr	TTC /	ATT Ile	GGC 1 Gly 1	TAC A Tyr 1	AAG Lys	GAG Glu	CGG Arg	864
50		CAG Gln 290	GAT Asp	GTG Val	GAC Asp	GIII	CGT Arg 295	GAG (GCT (CCC (Pro 1	Leu .	AAC A Asn A	AAC I	TTC Phe	TCT Ser	GTG Val	912
55	GCG Ala 305	CAG Gln	TGC Cys	CAG Gln	CTG Leu	ATG . Met : 310	AAG :	ACG (Thr (GAG (Arg E	Pro 2	CGG C Arg P	CC A	AC . sn '	ACC Thr	TTC Phe 320	960
	ATC 2	ATC	CGC	TGC	CTG	CAG '	rgg 1	ACC A	ACT (STC A	ATC (GAA C	GC A	.cc :	rtc	CAT	1008

										285							
	Ile	Ile	Arg	Cys	Leu 325	Gln	Trp	Thr	Thr	Val 330	Ile	Glu	Arg	Thr	Phe 335	His	
5												ACC Thr					1056
10												GAG Glu					1104
15												GAG Glu 380		_	_		1152
15												GAG Glu		_			1200
20												ATC Ile		_			1248
25												CTC Leu					1296
30												ACC Thr					1344
												CTG Leu 460					1392
35												TAC Tyr					1440
40												TTC Phe		_			1488
45												CTG Leu					1536
50												CTG Leu					1584
												TTC Phe 540					1632
55	GAG	GGG	ATC	AAG	GAC	GGT	GCC	ACC	ATG	AAG	ACC	TTT	TGC	GGC	ACA	сст	1680 2

										286							
	Glu 545	Gly	/ Ile	Lys	asp	Gly 550	Ala	Thr	Met	Lys	555		Cys	Gly	Thr	Pro 560	
5	GAG Glu	ТАС	CTG Leu	GCC Ala	Pro	GAG Glu	GTG Val	CTG Leu	GAG Glu	GAC Asp 570	Asn	GAC Asp	TAC Tyr	GGC Gly	CGT Arg 575	GCA Ala	1728
10	GTG Val	GAC Asp	TGG Trp	TGG Trp 580	GTA	CTG Leu	GGC	GTG Val	GTC Val 585	ATG Met	TAC Tyr	GAG Glu	ATG Met	ATG Met 590	TGC Cys	GGT Gly	1776
15	Arg	Leu	Pro 595	Phe	Tyr	Asn	Gln	Asp 600	His	Glu	Lys	Leu	Phe 605	Glu	Leu	Ile	1824
	Leu	мет 610		Glu	Ile	Arg	Phe 615	Pro	Arg	Thr	Leu	Gly 620	Pro	Glu	Ala	Lys	1872
20	625	Leu	CTT Leu	Ser	Gly	Leu 630	Leu	Lys	Lys	Asp	Pro 635	Lys	Gln	Arg	Leu	Gly 640	1920
25	GIY	GIY	TCC Ser	Glu	Asp 645	Ala	Lys	Glu	Ile	Met 650	Gln	His	Arg	Phe	Phe 655	Ala	1968
30	GIY	11e	GTG Val	660	Gln	His	Val	Tyr	Glu 665	Lys	Lys	Leu	Ser	Pro 670	Pro	Phe	2016
35	AAG Lys	CCC Pro	CAG Gln 675	GTC Val	ACG Thr	TCG Ser	GAG Glu	ACT Thr 680	GAC Asp	ACC Thr	AGG Arg	TAT Tyr	TTT Phe 685	GAT Asp	GAG Glu	GAG Glu	2064
	TTC Phe	ACG Thr 690	GCC Ala	CAG Gln	ATG Met	ATC Ile	ACC Thr 695	ATC Ile	ACA Thr	CCA Pro	CCT Pro	GAC Asp 700	CAA Gln	GAT Asp	GAC Asp	AGC Ser	2112
40	ATG Met 705	GAG Glu	TGT Cys	GTG Val	Asp	AGC Ser 710	GAG Glu	CGC Arg	AGG Arg	CCC Pro	CAC His 715	TTC Phe	CCC Pro	CAG Gln	TTC Phe	TCC Ser 720	2160
45	TAC Tyr	TCG Ser	GCC Ala	AGC Ser	AGC Ser 725	ACG Thr	GCC Ala	TGA									2184
50		(i) SE	QUEN	CE C	HARA	CTER	SEQ ISTI	CS:	NO:1	39:						
55			(B)	TYPE STRA	TH: : am NDED LOGY	ino NESS	acid : si	ngle	ids								

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(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:139:

5		,-	, .	J_Q01	21.02	225		11011	. 52,	, 10						
	Met 1	Val	Ser	Lys	Gly 5	Glu	Glu	Leu	Phe	Thr 10	Gly	Val	Val	Pro	Ile 15	Leu
				Asp 20	_	-			25		•			30		-
10		_	35	Gly	_			40	-	-			45	-		
	-	50		Gly	_		55			-		60				
15	65			Gly		70					75					80
				Phe	85					90					95	
				Phe 100					105		_	_		110		
20			115	Glu				120					125			
		130		Lys		_	135				-	140	•			_
25	145	-		Ser		150		_			155	-	-		•	160
				Val	165					170					175	
				Ala 180			_		185					190		
30			195	Leu		-		200	-				205			
		210	_	Pro			215	_	_			220				
35	225			Ala		230					235					240
	_		_	Ser	245	-				250					255	
40				His 260	_		_		265		_		_	270		_
40			275	Leu	_		_	280				_	285	_		
		290	_	Val	_		295					300				
45	305			Gln		310	_				315					320
			_	Сув	325					330					335	
5 0				Pro 340					345					350		
50			355	Gly		_	_	360					365	_		_
		370		Pro		_	375		_			380				
55	385			Pro		390	_				395				_	400
	ГÀЗ	Leu	Leu	Gly	Lys	Gly	Thr	Phe	Gly	Lys	Val	Ile	Leu	Val	Lys	Glu

288

	_				405					410					415	
				420	,				425					430		Val
5	Ile	Val	Ala 435	Lys	Asp	Glu	Val	Ala 440		Thr	Leu	Thr	Glu 445		Arg	Val
	Leu	Gln 450	Asn	Ser	Arg	His	Pro 455	Phe	Leu	Thr	Ala	Leu 460	Lys	Tyr	Ser	Phe
	Gln 465	Thr	His	Asp	Arg	Leu 470	Cys		Val	Met	Glu 475	Tyr	Ala	Asn	Gly	Gly
10			Phe	Phe	His 485			Arg	Glu		Val	Phe	Ser	Glu		480 Arg
	Ala	Arg	Phe	Tyr 500	Gly	Ala	Glu	Ile	Val 505	490 Ser	Ala	Leu	Asp		495 Leu	His
15	Ser	Glu	Lys 515			Val	Tyr	Arg 520	Asp	Leu	Lys	Leu	Glu 525	510 Asn	Leu	Met
	Leu	Asp 530		Asp	Gly	His	Ile 535	Lys		Thr	Asp	Phe 540	Gly	Leu	Cys	Lys
	Glu 545	Gly	Ile	Lys	Asp	Gly 550			Met	Lys	Thr 555	Phe	Cys	Gly	Thr	
20	Glu	Tyr	Leu	Ala	Pro 565		Val	Leu	Glu	Asp 570	Asn	Asp	Tyr	Gly	Arg 575	560 Ala
	Val	Asp	Trp	Trp 580		Leu	Gly	Val	Val 585	Met	Tyr	Glu	Met	Met 590	Cys	Gly
25	Arg	Leu	Pro 595	Phe	Tyr	Asn	Gln	Asp	His	Glu	Lys	Leu	Phe 605	Glu	Leu	Ile
	Leu	Met 610	Glu	Glu	Ile	Arg	Phe 615		Arg	Thr	Leu	Gly 620	Pro	Glu	Ala	Lys
	Ser 625	Leu	Leu	Ser	Gly	Leu 630		Lys	Lys	Asp	Pro 635	Lys	Gln	Arg	Leu	Gly 640
30	Gly	Gly	Ser	Glu	Asp 645	Ala	Lys	Glu	Ile	Met 650	Gln	His	Arg	Phe	Phe 655	Ala
	Gly	Ile	Val	Trp 660	Gln	His	Val	Tyr	Glu 665	Lys	Lys	Leu	Ser	Pro 670	Pro	Phe
35	Lys	Pro	Gln 675	Val	Thr	Ser	Glu	Thr 680		Thr	Arg	Tyr	Phe 685	Asp	Glu	Glu
		690					695					Asp 700	Gln			
	Met 705	Glu	Cys	Val	Asp	Ser 710	Glu	Arg	Arg	Pro	His 715	Phe	Pro	Gln	Phe	Ser 720
40	Tyr	Ser	Ala	Ser	Ser 725	Thr	Ala									
			(2)	INF	ORMA	TION	FOR	SEQ	ID	NO:1	40:					
45			٠													
40		(1) SE	QUEN LENC	CE C	HARA	CTER	ISTI	CS:							
			(B)	TYPE	: nu	clei	c ac	e pa	irs							
			(C)	STRA	NDED	NESS	: si	nale								
			(D)	TOPO	LOGY	: li	near									
50			• • • • •													
			i) M x) F			TYPE	: cD	NA								
			(A)	NAM	E/KE	Y: C	odin	g Se	quen	ce						
55			(B)	LOC	ATIO ER I	N: 1	2	391								

(D) OTHER INFORMATION:

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:140:

5		GAC Asp															48
10		GGC Gly			_	_	_										96
15		TTC Phe															144
		AGG Arg 50															192
20		TAC Tyr															240
25		CCT Pro															288
30		GGC Gly															336
35		CAG Gln															384
		ATC Ile 130															432
40	_	GAA Glu	_	_		_											480
45	Phe	CAG Gln	Val	Thr	Val 165	Arg	Asp	Pro	Ser	Gly 170	Arg	Pro	Leu	Arg	Leu 175	Pro	528
50	Pro	GTC Val	Leu	Pro 180	His	Pro	Ile	Phe	Asp 185	Asn	Arg	Ala	Pro	Asn 190	Thr	Ala	576
55	Glu	CTC Leu	Lys 195	Ile	Cys	Arg	Val	Asn 200	Arg	Asn	Ser	Gly	Ser 205	Сув	Leu	Gly	624
	GGG	GAT	GAG	ATC	TTC	CTA	CTG	TGT	GAC	AAG	GTG	CAG	AAA	GAG	GAC	ATT	672 2

										290							
	Gl	y As 21	p Gl 0	u Il	e Ph	e Lei	1 Let 21!	и Су: 5	s Asp	Lys	s Val	l Gln 220		Gl:	ı Ası	p Ile	
5	GA(Gl: 225	ı va	G TA	T TTO	C ACC	G GGA r Gly 230	Pro	A GGG	C TGO Y Trp	GAC Glu	G GCC 1 Ala 235	a Arg	GGC	TCC Ser	TTT	T TCG Ser 240	720
10	GIT	1 A1.	a As _l	o Va.	L His 245	s Arg	, Glr	ı Va]	l Ala	11e 250	Val	l Phe	Arg	Thr	255		768
15	Tyr	AL	a Asp	260	Ser	. Leu	Gln	ı Ala	265	Val	Arg	GTC Val	Ser	Met 270	Glr	Leu	816
	CGG Arg	CG(9 Pro 275	Ser	GAC Asp	CGG Arg	GAG Glu	Leu 280	Ser	GAG Glu	CCC Pro	ATG Met	GAA Glu 285	TTC	CAG Gln	TAC	864
20	CTG Leu	Pro 290	Asp	ACA Thr	GAC Asp	GAT Asp	CGT Arg 295	His	CGG Arg	ATT Ile	GAG Glu	GAG Glu 300	AAA Lys	CGT Arg	AAA Lys	AGG Arg	912
25	ACA Thr 305	туг	GAG	ACC Thr	TTC Phe	AAG Lys 310	AGC Ser	ATC Ile	ATG Met	AAG Lys	AAG Lys 315	AGT Ser	CCT Pro	TTC Phe	AGC Ser	GGA Gly 320	960
30	CCC Pro	ACC Thr	GAC Asp	CCC Pro	CGG Arg 325	CCT Pro	CCA Pro	CCT Pro	CGA Arg	CGC Arg 330	ATT Ile	GCT Ala	GTG Val	CCT Pro	TCC Ser 335	CGC Arg	1008
35	AGC Ser	TCA Ser	GCT Ala	TCT Ser 340	GTC Val	CCC Pro	AAG Lys	CCA Pro	GCA Ala 345	CCC Pro	CAG Gln	CCC Pro	TAT Tyr	CCC Pro 350	TTT Phe	ACG Thr	1056
	TCA Ser	TCC Ser	CTG Leu 355	AGC Ser	ACC Thr	ATC Ile	AAC Asn	TAT Tyr 360	GAT Asp	GAG Glu	TTT Phe	CCC Pro	ACC Thr 365	ATG Met	GTG Val	TTT Phe	1104
40	CCT Pro	TCT Ser 370	GGG Gly	CAG Gln	ATC Ile	AGC Ser	CAG Gln 375	GCC Ala	TCG Ser	GCC Ala	TTG Leu	GCC Ala 380	CCG Pro	GCC Ala	CCT Pro	CCC Pro	1152
45	CAA Gln 385	GTC Val	CTG Leu	CCC Pro	CAG Gln	GCT Ala 390	CCA Pro	GCC Ala	CCT Pro	GCC Ala	CCT Pro 395	GCT Ala	CCA Pro	GCC Ala	ATG Met	GTA Val 400	1200
50	TCA Ser	GCT Ala	CTG Leu	GCC Ala	CAG Gln 405	GCC Ala	CCA Pro	GCC Ala	Pro	GTC Val 410	CCA Pro	GTC (CTA Leu	GCC Ala	CCA Pro 415	GGC Gly	1248
55	CCT Pro	CCT Pro	CAG Gln	GCT Ala 420	GTG Val	GCC Ala	CCA Pro	CCT Pro	GCC Ala 425	CCC Pro	AAG Lys	CCC /	Thr	CAG Gln 430	GCT Ala	GGG Gly	1296
	GAA	GGA	ACG	CTG	TCA	GAG	GCC	CTG	CTG	CAG	CTG	CAG T	TTT (GAT	GAT	GAA	1344 2 90

										291							
	Glu	Gly	Thr 435	Leu	Ser	Glu	Ala	Leu 440	Leu	Gln	Leu	Gln	Phe 445	Asp	Asp	Glu	
5								AAC Asn									1392
10								TCC Ser									1440
15								ACA Thr									1488
								GTG Val									1536
20								GCC Ala 520									1584
25								TCC Ser								_	1632
30								TTG Leu									1680
35								ACC Thr									1728
								CAC His									1776
40	_	_		_	_		_	AAG Lys 600						_		_	1824
45								TGG Trp									1872
50								CGC Arg									1920
EE								CCC Pro		_							1968
55	ATC	TTC	TTC	AAG	GAC	GAC	GGC	AAC	TAC	AAG	ACC	CGC	GCC	GAG	GTG	AAG	2016

										292							
	Ile	Phe	Phe	660	Asp	Asp	Gly	Asn	Tyr 665		Thr	Arg	Ala	Glu 670		Lys	
5	TT(Phe	GAG Glu	GGC Gly 675	GAC Asp	ACC Thr	CTG Leu	GTG Val	AAC Asn 680	Arg	ATC	GAG Glu	CTG Leu	AAG Lys 685	GGC Gly	ATC	GAC Asp	2064
10	Pne	690	Glu	GAC Asp	Gly	Asn	Ile 695	Leu	Gly	His	Lys	Leu 700	Glu	Tyr	Asn	Tyr	2112
15	705	ser	His	AAC Asn	Val	Tyr 710	Ile	Met	Ala	Asp	Lys 715	Gln	Lys	Asn	Gly	Ile 720	2160
	гàа	val	Asn	TTC Phe	Lys 725	Ile	Arg	His	Asn	Ile 730	Glu	Asp	Gly	Ser	Val 735	Gln	2208
20	CTC Leu	GCC Ala	GAC Asp	CAC His 740	TAC Tyr	CAG Gln	CAG Gln	AAC Asn	ACC Thr 745	CCC Pro	ATC Ile	GGC Gly	GAC Asp	GGC Gly 750	CCC Pro	GTG Val	2256
25	CTG Leu	CTG Leu	CCC Pro 755	GAC Asp	AAC Asn	CAC His	TAC Tyr	CTG Leu 760	AGC Ser	ACC Thr	CAG Gln	TCC Ser	GCC Ala 765	CTG Leu	AGC Ser	AAA Lys	2304
30	GAC Asp	CCC Pro 770	AAC Asn	GAG Glu	AAG Lys	CGC Arg	GAT Asp 775	CAC His	ATG Met	GTC Val	CTG Leu	CTG Leu 780	GAG Glu	TTC Phe	GTG Val	ACC Thr	2352
35	GCC Ala 785	GCC Ala	GGG Gly	ATC Ile	Thr	CTC Leu 790	GGC Gly	ATG Met	GAC Asp	GAG Glu	CTG Leu 795	TAC Tyr	AAG Lys	TAA			2394
			(2)	INF	ORMA	TION	FOR	SEC	ID	NO:1	41:						
40		(i	(A) (B) (C)	QUEN LENG TYPE STRA TOPO	TH: : am NDED	797 ino NESS	amin acid : si	o ac ngle	ids							·	
45		(₹) FR	OLEC AGME	NT T	YPE:	int	erna	1								
		(х	i) S	EQUE	NCE 1	DESC	RIPT	ION:	SEQ	ID 1	NO:1	41:					
50	Met 1				5					10					15		
	Ser			20					25				•	Arg	Gly 1		
55	Arg		33					40					Ser :	lle :			
	Glu .	J '			-sp	HIE !	inr l	ьуs '	inr l	HIS]	ro?	rhr]	lle I	ys :	Ile A	Asn	

		E 0					e e					60				
	C117	50	Thr	Clv	Dro	Cl v	55 ™h~	V-1	7.20	Tla	Co~	60 Leu	17.7	Thr	T 1/0	Λen
	65	TYL	1111	GIY	PIO	70	1111	vai	ALG	116	75	пец	val	1111	пуъ	80 80
		Dro	ніс	Δra	Pro		Pro	Hic	Glu	I.e.ii		Gly	Lve	Δen	Cve	
5	110	110	1113	A. g	85		110	1113	O.L.u	90	vai	Gry	цуз	ASP	95	Arg
J	Asn	Glv	Phe	Tvr		Δla	Glu	Len	Cvs		Asn	Arg	Cvs	Tle		Ser
		017	1110	100				u	105		1102	**** 5	-,5	110		502
	Phe	Gln	Asn		Glv	Ile	Gln	Cvs		Lvs	Lvs	Arg	Asp		Glu	Gln
			115		1			120		1	-,-	3	125			
10	Ala	Ile		Gln	Arq	Ile	Gln		Asn	Asn	Asn	Pro	_	Gln	Val	Pro
		130			_		135					140				
	Ile	Glu	Glu	Gln	Arg	Gly	Asp	Tyr	qaA	Leu	Asn	Ala	Val	Arg	Leu	Сув
	145					150					155					160
	Phe	Gln	Val	Thr	Val	Arg	Asp	Pro	Ser	Gly	Arg	Pro	Leu	Arg	Leu	Pro
15					165					170					175	
	Pro	Val	Leu	Pro	His	${\tt Pro}$	Ile	Phe	Asp	Asn	Arg	Ala	Pro	Asn	Thr	Ala
				180					185					190		
	Glu	Leu	Lys	Ile	Cys	Arg	Val	Asn	Arg	Asn	Ser	Gly	Ser	Cys	Leu	Gly
			195					200					205			
20	Gly	-	Glu	Ile	Phe	Leu		Cys	Asp	Lys	Val	Gln	Lys	Glu	Asp	Ile
		210	_				215		_			220		_		_
		Val	Tyr	Phe	Thr	_	Pro	Gly	Trp	Glu		Arg	Gly	Ser	Phe	
	225		•	77 - 7	TT 4 =	230	0 1	** . 3		~ 1	235	-1	_		n	240
25	GIN	АТА	Asp	vaı	H15	Arg	GIn	vai	Ата		vaı	Phe	Arg	Thr		Pro
23	Tree	712	λen	Dro		T.011	Gln	λla	Dro	250 Val	7~~	Val	Car	Mot	255	T.633
	IYL	Ala	дал	260	361	пец	GIII	міа	265	vai	Arg	vai	SEL	270	GIII	Deu
	Ara	Ara	Pro		Asp	Ara	Glu	Leu		Glu	Pro	Met	Glu		Gln	Tvr
		5	275			9		280					285			-1-
30	Leu	Pro	Asp	Thr	Asp	Asp	Arg	His	Arg	Ile	Glu	Glu	Lys	Arg	Lys	Arg
		290	_		-		295		_			300	-	_	-	_
	Thr	Tyr	Glu	Thr	Phe	Lys	Ser	Ile	Met	Lys	Lys	Ser	Pro	Phe	Ser	Gly
	305				•	310					315					320
	Pro	Thr	Asp	Pro	Arg	Pro	Pro	Pro	Arg	Arg	Ile	Ala	Val	Pro	Ser	Arg
35					325					330					335	_
	Ser	Ser	Ala		Val	Pro	Lys	Pro		Pro	Gln	Pro	Tyr		Phe	Thr
	_	_	_	340			_	_	345	_				350		
	ser	Ser		Ser	Thr	iiе	Asn	-	Asp	Glu	Phe	Pro		Met	Val	Phe
40	Desa	0	355	a 3	T1.	C	71 -	360	0	77.		77 -	365	n 1	D	Dwo
40	PIO	370	GIA	GIII	116	ser	375	AIA	ser	Ата	Leu	Ala 380	PIO	Ala	PIO	PIO
	Gln		Len	Dro	Gln	λla		λla	Dro	λl ¬	Dro	Ala	Dro	7 l n	Mat	Val
	385	vai	БСи	110	OIII	390	110	AIG	FIO	AIG	395	AIG	FIU	AIG	I-IC C	400
		Ala	Leu	Ala	Gln		Pro	Ala	Pro	Val		Val	Leu	Ala	Pro	
45					405					410			200		415	1
	Pro	Pro	Gln	Ala	Val	Ala	Pro	Pro	Ala		Lys	Pro	Thr	Gln	Ala	Gly
				420					425		-			430		_
	Glu	Gly	Thr	Leu	Ser	Glu	Ala	Leu	Leu	Gln	Leu	Gln	Phe	Asp	Asp	Glu
			435					440					445			
50	Asp	Leu	Gly	Ala	Leu	Leu	Gly	Asn	Ser	Thr	Asp	Pro	Ala	Val	Phe	Thr
		450					455					460				
	_	Leu	Ala	Ser	Val	-	Asn	Ser	Glu	Phe		Gln	Leu	Leu	Asn	
	465		_			470					475					480
EE	Gly	Ile	Pro	Val		Pro	His	Thr	Thr		Pro	Met	Leu	Met		Tyr
55	D	~ 3	n1-	T7 -	485	3		*** 3	m)	490		03		-	495	
	Pro	GIU	Ala	тте	inr	arg	ьeu	val	Inr	ыцу	ΑΙа	uLى	arg	rro	Pro	Asp

```
500
                                       505
       Pro Ala Pro Ala Pro Leu Gly Ala Pro Gly Leu Pro Asn Gly Leu Leu
                                  520
       Ser Gly Asp Glu Asp Phe Ser Ser Ile Ala Asp Met Asp Phe Ser Ala
  5
                              535
                                                 540
       Leu Leu Ser Gln Ile Ser Ser Leu Asp Pro Pro Val Ala Thr Met Val
                           550
                                           555
       Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu Val Glu
                      565
                                          570
       Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly Glu Gly
 10
                   580
                                     585
       Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile Cys Thr
                                  600
                                                     605
       Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr Leu Thr
 15
                             615
       Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys Gln His
                   630
                                             635
       Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu Arg Thr
                                650
 20
      Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu Val Lys
      Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly Ile Asp
             675
                                  680
      Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr Asn Tyr
25
                           695
      Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn Gly Ile
                       710
                                             715
      Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser Val Gln
                     725
                                          730
      Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly Pro Val
30
                 740
                                    745
      Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu Ser Lys
                                760
                                                   765
      Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe Val Thr
35
                              775
                                                780
      Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys
                         790
               (2) INFORMATION FOR SEQ ID NO:142:
40
            (i) SEQUENCE CHARACTERISTICS:
              (A) LENGTH: 2394 base pairs
              (B) TYPE: nucleic acid
              (C) STRANDEDNESS: single
45
              (D) TOPOLOGY: linear
            (ii) MOLECULE TYPE: CDNA
            (ix) FEATURE:
50
               (A) NAME/KEY: Coding Sequence
               (B) LOCATION: 1...2391
               (D) OTHER INFORMATION:
            (xi) SEQUENCE DESCRIPTION: SEQ ID NO:142:
55
     ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG
```

										295							
	Met 1	Val	Ser	Lys	Gly 5	Glu	Glu	Leu	Phe	Thr 10	Gly	Val	Val	Pro	Ile 15	Leu	
5					GGC Gly												96
10					GAT Asp											_	144
45					AAG Lys												192
15					GTG Val	_								_			240
20					TTC Phe 85												288
25					TTC Phe												336
30					GGC Gly											_	384
25					GAG Glu										_		432
35					CAC His												480
40					AAC Asn 165												528
45					GAC Asp												576
50					CCC Pro												624
EE					AAC Asn												672
55	GTG	ACC	GCC	GCC	GGG	ATC	ACT	CTC	GGC	ATG	GAC	GAG	CTG	TAC	AAG	TCC	720

										296							
	Va: 22!	l Thi	r Ala	Ala	a Gly	/ Ile 230	Thr	Leu	ı Gly	/ Met	235		ı Le	и Ту:	r Ly	s Ser 240	
5	GG!	A CTO	AGA Arg	TC7	CGA Arg 245	Ala	ATG Met	GAC Asp	GAA Glu	Leu 250	Phe	C CCC	C CTO	C ATO	25!	C CCG Pro	768
10	GCA Ala	A GAG	CCA Pro	GCC Ala 260	GIn	GCC Ala	TCT Ser	Gly	Pro	Tyr	GTG Val	GAC Glu	ATO	270 270	e Glı	G CAG	816
15	Pro	AAG Lys	CAG Gln 275	CGG Arg	GGC Gly	ATG Met	CGC Arg	Phe 280	Arg	TAC	AAG Lys	TGC Cys	GA0 Glu 285	ı Gly	G CGC	TCC Ser	864
	GCG Ala	GGC Gly 290	AGC Ser	ATC Ile	CCA Pro	GGC Gly	GAG Glu 295	AGG Arg	AGC Ser	ACA Thr	GAT Asp	ACC Thr 300	Thr	AAC Lys	ACC Thr	CAC His	912
20	CCC Pro 305	Thr	ATC Ile	AAG Lys	ATC Ile	AAT Asn 310	GGC Gly	TAC Tyr	ACA Thr	GGA Gly	CCA Pro 315	GGG Gly	ACA Thr	GTG Val	CGC Arg	ATC Ile 320	960
25	TCC Ser	CTG Leu	GTC Val	ACC Thr	AAG Lys 325	GAC Asp	CCT Pro	CCT Pro	CAC His	CGG Arg 330	CCT Pro	CAC His	CCC Pro	CAC His	GAG Glu 335	Leu	1008
30	GTA Val	GGA Gly	AAG Lys	GAC Asp 340	TGC Cys	CGG Arg	GAT Asp	GGC Gly	TTC Phe 345	TAT Tyr	GAG Glu	GCT Ala	GAG Glu	CTC Leu 350	TGC Cys	CCG Pro	1056
35	GAC Asp	CGC Arg	TGC Cys 355	ATC Ile	CAC His	AGT Ser	TTC Phe	CAG Gln 360	AAC Asn	CTG Leu	GGA Gly	ATC Ile	CAG Gln 365	TGT Cys	GTG Val	AAG Lys	1104
	AAG Lys	CGG Arg 370	GAC Asp	CTG Leu	GAG Glu	CAG Gln	GCT Ala 375	ATC Ile	AGT Ser	CAG Gln	CGC Arg	ATC Ile 380	CAG Gln	ACC Thr	AAC Asn	AAC Asn	1152
40	AAC Asn 385	CCC Pro	TTC Phe	CAA Gln	vai	CCT Pro 390	ATA Ile	GAA Glu	GAG Glu	CAG Gln	CGT Arg 395	GGG Gly	GAC Asp	TAC Tyr	GAC Asp	CTG Leu 400	1200
45	AAT Asn	GCT Ala	GTG Val	Arg	CTC Leu 405	TGC Cys	TTC Phe	CAG Gln	Val	ACA Thr 410	GTG Val	CGG Arg	GAC Asp	CCA Pro	TCA Ser 415	GGC Gly	1248
50	AGG Arg	CCC Pro	CTC Leu	CGC Arg 420	CTG Leu	CCG Pro	CCT Pro	Val	CTT Leu 425	CCT Pro	CAT His	CCC Pro	ATC Ile	TTT Phe 430	GAC Asp	AAT Asn	1296
55	CGT Arg	Ата	CCC A Pro A 435	AAC Asn	ACT (GCC (Glu :	CTC Leu 440	AAG Lys	ATC Ile	TGC Cys	CGA Arg	GTG Val 445	AAC Asn	CGA Arg	AAC Asn	1344
	TCT	GGC .	AGC T	rgc	CTC (GGT (GGG (GAT (GAG :	ATC	TTC	CTA	CTG	TGT	GAC	AAG	1392 2 96

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	Ser	Gly 450	Ser	Cys	Leu	Gly	Gly 455	Asp	Glu	Ile	Phe	Leu 460	Leu	Сув	Asp	Lys		
5					GAC Asp												1440	
10					TTT Phe 485												1488	
15					CCT Pro												1536	
13					CAG Gln												1584	
20					CAG Gln												1632	
25					AAA Lys												1680	
30					AGC Ser 565												1728	
35					TCC Ser												1776	
					TTT Phe												1824	
40					GTG Val												1872	
45					CCT Pro												1920	
50					ATG Met 645												1968	
55					CCA Pro												2016	
55	AAG	ccc	ACC	CAG	GCT	GGG	GAA	GGA	ACG	CTG	TCA	GAG	GCC	CTG	CTG	CAG	2064	2

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	Lys	Pro	Thr 675	Gln	Ala	Gly	Glu	Gly 680		Leu	Ser	Glu	Ala 685	Leu	Leu	Gln	
5	CTG Leu	CAG Gln 690	TTT Phe	GAT Asp	GAT Asp	GAA Glu	GAC Asp 695	CTG Leu	GGG Gly	GCC Ala	TTG Leu	CTT Leu 700	GGC Gly	AAC Asn	AGC Ser	ACA Thr	2112
10	GAC Asp 705	CCA Pro	GCT Ala	GTG Val	TTC Phe	ACA Thr 710	GAC Asp	CTG Leu	GCA Ala	TCC Ser	GTC Val 715	GAC Asp	AAC Asn	TCC Ser	GAG Glu	TTT Phe 720	2160
15	CAG Gln	CAG Gln	CTG Leu	CTG Leu	AAC Asn 725	CAG Gln	GGC Gly	ATA Ile	CCT Pro	GTG Val 730	GCC Ala	CCC Pro	CAC His	ACA Thr	ACT Thr 735	GAG Glu	2208
	CCC Pro	ATG Met	CTG Leu	ATG Met 740	GAG Glu	TAC Tyr	CCT Pro	GAG Glu	GCT Ala 745	ATA Ile	ACT Thr	CGC Arg	CTA Leu	GTG Val 750	ACA Thr	GGG Gly	2256
20	GCC Ala	CAG Gln	AGG Arg 755	CCC Pro	CCC Pro	GAC Asp	CCA Pro	GCT Ala 760	CCT Pro	GCT Ala	CCA Pro	CTG Leu	GGG Gly 765	GCC Ala	CCG Pro	GGG Gly	2304
25	CTC Leu	CCC Pro 770	AAT Asn	GGC Gly	CTC Leu	CTT Leu	TCA Ser 775	GGA Gly	GAT Asp	GAA Glu	GAC Asp	TTC Phe 780	TCC Ser	TCC Ser	ATT Ile	GCG Ala	2352
30	GAC Asp 785	ATG Met	GAC Asp	TTC Phe	TCA Ser	GCC Ala 790	CTG Leu	CTG Leu	AGT Ser	CAG Gln	ATC Ile 795	AGC Ser	TCC Ser	TAA			2394
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	Arg	Thr	Ile	Phe 100	Phe	Lys	Asp	Asp	Gly 105	Asn	Tyr	Lys	Thr	Arg 110	Ala	Glu
5	Val	Lys	Phe		Gly	Asp	Thr	Leu 120		Asn	Arg	Ile	Glu 125	Leu	Lys	Gly
	Ile	Asp 130	Phe	Lys	Glu	Asp	Gly 135	Asn	Ile	Leu	Gly	His 140	Lys	Leu	Glu	Tyr
	Asn 145	Tyr	Asn	Ser	His	Asn 150	Val	Tyr	Ile	Met	Ala 155	Asp	Lys	Gln	Lys	Asn 160
10	Gly	Ile	Lys	Val	Asn 165	Phe	Lys	Ile	Arg	His 170	Asn	Ile	Glu	Asp	Gly 175	Ser
	Val	Gln	Leu	Ala 180	Asp	His	Tyr	Gln	Gln 185	Asn	Thr	Pro	Ile	Gly 190	Asp	Gly
15	Pro	Val	Leu 195	Leu	Pro	Asp	Asn	His 200	Tyr	Leu	Ser	Thr	Gln 205	Ser	Ala	Leu
	Ser	Lys 210	Asp	Pro	Asn	Glu	Lys 215	Arg	Asp	His	Met	Val 220	Leu	Leu	Glu	Phe
	Val 225	Thr	Ala	Ala	Gly	Ile 230	Thr	Leu	Gly	Met	Asp 235	Glu	Leu	Tyr	Lys	Ser 240
20	Gly	Leu	Arg	Ser	Arg 245	Ala	Met	qaA	Glu	Leu 250	Phe	Pro	Leu	Ile	Phe 255	Pro
	Ala	Glu	Pro	Ala 260	Gln	Ala	Ser	Gly	Pro 265	Tyr	Val	Glu	Ile	Ile 270	Glu	Gln
25	Pro	Lys	Gln 275	Arg	Gly	Met	Arg	Phe 280	Arg	Tyr	Lys	Cys	Glu 285	Gly	Arg	Ser
	Ala	Gly 290	Ser	Ile	Pro	Gly	Glu 295	Arg	Ser	Thr	Asp	Thr 300	Thr	Lys	Thr	His
	Pro 305	Thr	Ile	Lys	Ile	Asn 310	Gly	Tyr	Thr	Gly	Pro 315	Gly	Thr	Val	Arg	Ile 320
30	Ser	Leu	Val	Thr	Lys 325	Asp	Pro	Pro	His	Arg 330	Pro	His	Pro	His	Glu 335	Leu
		_	_	340	_	_	_	_	345	-				Leu 350	_	
35			355					360					365	Cys		
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45	-		435					440	-		_	_	445	Asn		
		450		-		_	455	-				460		Cys	_	
50	465		_		_	470			-		475			Gly	_	480
50 -		_	_		485				_	490				Val	495	
				500			_		505					Ala 510		
55			515					520					525	Leu		
	Pro	met	GIU	rne	GTU	ıyr	ren	Pro	Asp	ınr	Asp	ASP	Arg	His	arg	116

		530					535					540	1			
	Glu	Glu	Lys	Arg	Lys	Arg	Thr	Tyr	Glu	Thr	Phe	Lvs	Ser	Ile	Met	Lvs
	545					550					555					560
	Lys	Ser	Pro	Phe	Ser	Gly	Pro	Thr	Asp	Pro	Ara	Pro	Pro	Pro	Ara	Ara
5					565					570					575	
	Ile	Ala	Val	Pro	Ser	Arg	Ser	Ser	Ala	Ser	Val	Pro	Lvs	Pro	Ala	Pro
				580					585					590		
	Gln	Pro	Tyr	Pro	Phe	Thr	Ser	Ser	Leu	Ser	Thr	Ile	Asn	Tyr	Asp	Glu
			595					600					605			
10	Phe	Pro	Thr	Met	Val	Phe	Pro	Ser	Gly	Gln	Ile	Ser	Gln	Ala	Ser	Ala
		610					615					620				
	Leu	Ala	Pro	Ala	Pro	Pro	Gln	Val	Leu	Pro	Gln	Ala	Pro	Ala	Pro	Ala
	625					630					635					640
15	Pro	Ala	Pro	Ala	Met	Val	Ser	Ala	Leu	Ala	Gln	Ala	Pro	Ala	Pro	Val
13	D	**- 7			645					650					655	
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20	I.611	Gln		700	N am	a 1	3	680					685			
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25					725	0111	Gry	116	PIO	730	Ата	Pro	HIS	Thr		Glu
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30	Leu	Pro	Asn	Gly	Leu	Leu	Ser	Gly	Asp	Glu	Asp	Phe	Ser	Ser	Tle	Δla
		770					775					780				
	Asp	Met	Asp	Phe	Ser	Ala	Leu	Leu	Ser	Gln	Ile	Ser	Ser			
	785					790					795					

CLAIMS

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- 1. A method for extracting quantitative information relating to an influence on a cellular response, the method comprising recording variation, caused by the influence on a mechanically intact living cell or mechanically intact living cells, in spatially distributed light emitted from a luminophore, the luminophore being present in the cell or cells and being capable of being redistributed in a manner which is related with the degree of the influence, and/or of being modulated by a component which is capable of being redistributed in a manner which is related to the degree of the influence, the association resulting in a modulation of the luminescence characteristics of the luminophore, and processing the recorded variation in the spatially distributed light to provide quantitative information correlating the spatial distribution to the degree of the influence on the cellular response.
- 2. A method according to claim 1, as used for extracting quantitative information relating to an influence on an intracellular pathway involving redistribution of at least one component associated with the pathway, or part thereof, the method comprising recording the result of the influence on mechanically intact living cell or cells, as manifested in spatially distributed light emitted from a luminophore which is present in the cell or cells and which is capable of being redistributed, by modulation of the pathway, in a manner which is related to the redistribution of the at least one component of the intracellular pathway, processing the recorded result to provide quantitative information about the spatially distributed light and correlating the quantitative information to the degree of the influence on the intracellular pathway.
- 3. A method according to claim 1 or 2, wherein the quantitative information which is indicative of the degree of the cellular response to the influence or the result of the influence on the intracellular pathway is extracted from the recording or recordings according to a predetermined calibration based on responses or results, recorded in the same manner, to known degrees of a relevant specific influence.
- 4. A method according to any of the preceding claims, wherein the influence is contact between the mechanically intact living cell or the group of mechanically intact living cells with a

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chemical substance and/or incubation of the mechanically intact living cell or the group of mechanically intact living cells with a chemical substance.

- 5. A method according to claim 4 wherein the substance is a substance whose effect on an intracellular pathway is to be determined.
 - 6. A method according to any of the preceding claims, wherein the recording is made at a single point in time after the application of the influence.
- 7. A method according to any of claims 1-5, wherein the recording is made at two points in time, one point being before, and the other point being after the application of the influence.
 - 8. A method according to any of claims 1-5, wherein the recording is performed at a series of points in time, in which the application of the influence occurs at some time after the first time point in the series of recordings, the recording being performed, e.g., with a predetermined time spacing of from 0.1 seconds to 1 hour, preferably from 1 to 60 seconds, more preferably from 1 to 30 seconds, in particular from 1 to 10 seconds, over a time span of from 1 second to 12 hours, such as from 10 seconds to 12 hours, e.g., from 10 seconds to one hour, such as from 60 seconds to 30 minutes or 20 minutes.

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- 9. A method according to any of claims 1-7, wherein the cell or cells is/are fixed at a point in time after the application of the influence at which the response has been predetermined to be significant, and the recording is made at an arbitrary later time.
- 25 10. A method according to any of the preceding claims, wherein the luminophore is a luminophore which is capable of being redistributed in a manner which is physiologically relevant to the degree of the influence.

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11. A method according to any of the preceding claims, wherein the luminophore is a luminophore which is capable of associating with a component which is capable of being redistributed in manner which is physiologically relevant to the degree of the influence.

- 12. A method according to any of the preceding claims, wherein the luminophore is a luminophore which is capable of being redistributed in a manner which is experimentally determined to be correlated to the degree of the influence.
- 13. A method according to any of the preceding claims, wherein the luminophore is a luminophore which is capable of being redistributed, by modulation of the intracellular pathway, in substantially the same manner as the at least one component of the intracellular pathway.
- 14. A method according to any of claims 1-13, wherein the luminophore is a luminophore which is capable of being quenched upon spatial association with a component which is redistributed by modulation of the pathway, the quenching being measured as a decrease in the intensity of the luminescence.

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- 15. A method according to any of claims 1-13, wherein the variation or result with respect to the spatially distributed light emitted by the luminophore is detected by a change in the resonance energy transfer between the luminophore and another luminescent entity capable of delivering energy to the luminophore, each of which has been selected or engineered to become part of, bound to or associated with particular components of the intracellular pathway, and one of which undergoes redistribution in response to the influence, thereby changing the amount of resonance energy transfer, the change in the resonance energy transfer being measured as a change in the intensity of emission from the luminophore.
- 16. A method according to claim 15, wherein the change in the intensity of the emission from the luminophore is sensed by a single channel photodetector which responds only to the average intensity of the luminophore in a non-spatially resolved fashion

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17. A method according to any of claims 1-16, wherein the property of the light being recorded is intensity, fluorescence lifetime, polarization, wavelength shift, or other property which is modulated as a result of the underlying cellular response.

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- 18. A method according to any of claims 1-15 or 17, wherein the recording of the spatially distributed light is performed using a recording system which records the spatial distribution of a recordable property of the light in the form of an ordered array of values.
- 19. A method according to claim 18, wherein the recording of the spatial distribution of the recordable property of the light is performed using a charge transfer device such as a CCD array or a vacuum tube device such as a vidicon tube.
- 20. A method according to any of the preceding claims, wherein the light to be measured
 passes through a filter which selects the desired component of the light to be measured and rejects other components.
 - 21. A method according to any of the preceding claims, wherein the recording of the spatial distribution of the recordable property of light is performed by fluorescence microscopy.

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- 22. A method according to any of the preceding claims, wherein the recording of the variation or result with respect to light emitted from the luminophore is performed by recording the spatially distributed light as one or more digital images, and the processing of the recorded variation to reduce it to one or more numbers representative of the degree of redistribution comprises a digital image processing procedure or combination of digital image processing procedures.
- 23. A method according to any of claims 2-22, wherein the intracellular pathway is an intracellular signalling pathway.

- 24. A method according to any of the preceding claims, wherein the luminophore is a fluorophore.
- 25. A method according to any of the preceding claims wherein the luminophore is a polypeptide encoded by and expressed from a nucleotide sequence harboured in the cell or cells.
- 26. A method according to any of the preceding claims, wherein the luminophore is a hybrid polypeptide comprising a fusion of at least a portion of each of two polypeptides one of which comprises a luminescent polypeptide and the other one of which comprises a biologically active polypeptide, as defined herein.
- 27. A method according to claim 26, wherein the luminescent polypeptide is a GFP as defined herein.
 - 28. A method according to claim 27 wherein the GFP is selected from the group consisting of green fluorescent proteins having the F64L mutation as defined herein.
- 29. A method according to claim 28 wherein the GFP is a GFP variant selected from the group consisting of F64L-GFP, F64L-Y66H-GFP, F64L-S65T-GFP, and EGFP.
 - 30. A method according to any of the previous claims for detecting intracellular translocation of a biologically active polypeptide affecting intracellular processes upon activation, the method comprising
 - a) culturing one or more cells containing a nucleotide sequence coding for a hybrid polypeptide comprising a GFP which is N- or C-terminally tagged, optionally through a linker, to a biologically active polypeptide under conditions permitting expression of the nucleotide sequence,

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- b) modulating the activity of the biologically active polypeptide by incubating the cell or cells with a substance having biological activity and
- c) measuring the fluorescence produced by the incubated cell or cells and determining the result or variation with respect to the fluorescence, such result or variation being indicative of the translocation of a biologically active polypeptide in said cell.
- 31. A method according to claim 30, wherein the nucleotide sequence is a DNA sequence.
- 32. A method according to claim 30 or 31, wherein the modulation is an activation.
- 33. A method according to claim 30 or 31, wherein the modulation is a deactivation.
- 34. A method according to any of claims 30-33 wherein the fluorescence of the cell or cells is measured prior to the modulation, and the result or variation determined in step (c) is a change in fluorescence compared to the fluorescence measured prior to the modulation.
 - 35. A method according to any of claims 30-34, wherein the intracellular processes are intracellular signalling pathways.
- 36. A method according to claim 34, wherein the change in fluorescence measured in step(c) comprises determining a change in the spatial distribution of the fluorescence.
 - 37. A method according to any of the preceding claims wherein the mechanically intact living cell or cells is/are a mammalian cell/mammalian cells which, during the time peroid over which the influence is observed, is/are incubated at a temperature of 30°C or above, preferably at a temperature of from 32°C to 39°C, more preferably at a temperature of from 35°C to 38°C, and most preferably at a temperature of about 37°C.

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38. A method according to any of the preceding claims, wherein the at least one mechanically intact living cell is part of a matrix of identical or non-identical cells.

- 39. A method according to any of claims 1-36 and 38, wherein the cell or cells is/are selected from the group consisting of fungal cells, such as a yeast cell; invertebrate cells including insect cells; and vertebrate cells, such as mammalian cells.
 - 40. A nucleic acid construct coding for a fusion polypeptide comprising a biologically active polypeptide that is a component of an intracellular signalling pathway, or a part thereof, and a GFP, with the proviso that the construct is not a construct coding for a fusion polypeptide in which the biologically active polypeptide is selected from the group consisting of PKC-alpha, PKC-gamma, and PKC-epsilon.
- 41. A nucleic acid construct coding for a fusion polypeptide comprising a biologically active polypeptide that is a component of an intracellular signalling pathway, or a part thereof, and an F64L mutant of GFP.
 - 42. A nucleic acid construct according to claim 40 or 41, wherein the biologically active polypeptide is a protein kinase or a phosphatase.

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- 43. A nucleic acid construct according to any of claims 40-42 wherein the GFP is N- or C-terminally tagged, optionally via a peptide linker, to the biologically active polypeptide or part thereof.
- 44. A nucleic acid construct according to any of claims 40, 41 and 43, wherein the biologically active polypeptide is a transcription factor or a part thereof which changes cellular localisation upon activation.

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- 45. A nucleic acid construct according to any of claims 40, 41 and 43, wherein the biologically active polypeptide is a protein, or a part thereof, which is associated with the cytoskeletal network and which changes cellular localisation upon activation.
- 46. A nucleic acid construct according to any of claims 40-43, wherein the biologically active polypeptide is a protein kinase or a part thereof which changes cellular localisation upon activation.
- 47. A nucleic acid construct according to claim 46, wherein the protein kinase is a serine/threonine protein kinase or a part thereof capable of changing intracellular localisation upon activation.

- 48. A nucleic acid construct according to claim 46, wherein the protein kinase is a tyrosine protein kinase or a part thereof capable of changing intracellular localisation upon activation.
- 49. A nucleic acid construct according to claim 46, wherein the protein kinase is a phospholipid-dependent serine/threonine protein kinase or a part thereof capable of changing intracellular localisation upon activation.
- 50. A nucleic acid construct according to claim 46, wherein the protein kinase is a cAMP-dependent protein kinase or a part thereof capable of changing cellular localisation upon activation.
- 51. A nucleic acid construct according to claim 50 which codes for a PKAc-F64L-S65T-GFP fusion.
 - 52. A nucleic acid construct according to claim 46, wherein the protein kinase is a cGMP-dependent protein kinase or a part thereof capable of changing cellular localisation upon activation.

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53. A nucleic acid construct according to claim 46, wherein the protein kinase is a calmodulin-dependent serine/threonine protein kinase or a part thereof capable of changing cellular localisation upon activation.

- 54. A nucleic acid construct according to claim 46, wherein the protein kinase is a mitogenactivated serine/threonine protein kinase or a part thereof capable of changing cellular localisation upon activation.
- 55. A nucleic acid construct according to claim 54, which codes for an ERK1-F64L-S65T-GFP fusion.
 - 56. A nucleic acid construct according to claim 54, which codes for an EGFP-ERK1 fusion.
- 57. A nucleic acid construct according to claim 46, wherein the protein kinase is a cyclindependent serine/threonine protein kinase or a part thereof capable of changing cellular localisation upon activation.
- 58. A nucleic acid construct according to claim 42 or 43, wherein the biologically active polypeptide is a protein phosphatase or a part thereof capable of changing cellular localisation upon activation.
 - 59. A nucleic acid construct according to any of claims 40-58 which is a DNA construct.
- 60. A nucleic acid construct according to any of claims 40-59 wherein the gene encoding GFP is derived from Aequorea victoria.
 - 61. A nucleic acid construct according to claim 60 in which the gene encoding GFP is the gene encoding EGFP as defined herein.

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62. A nucleic acid construct according to claim 60 in which the gene encoding a GFP is a gene encoding a GFP variant selected from F64L-GFP, F64L-Y66H-GFP and F64L-S65T-GFP.

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- 63. A DNA construct according to claim 59 and 61 or, where applicable, 62, which is a construct as identified by any of the DNA sequences shown in SEQ ID NO: 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, and 142, or is a variant thereof capable of encoding the same fusion polypeptide or a fusion polypeptide which is biologically equivalent thereto, as defined herein.
- 64. A cell containing a nucleic acid construct according to any of claims 40-63 and capable of expressing the sequence encoded by the construct.

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- 65. A cell according to claim 64, which is a eukaryotic cell.
- 66. A cell according to claim 64, which is selected from the group consisting of fungal cells, such as yeast cells; invertebrate cells, including insect cells, and vertebrate cells, such as mammalian cells.
- 67. A cell according to claim 66, which is a mammalian cell.
- 68. An organism carrying in at least one of its component cells a nucleic acid sequence as contained in the constructs according to any of claims 40-59, said cell being capable of expressing said nucleic acid sequence.
- 69. An organism according to claim 68 which is selected from the group consisting of unicellular and multicellular organisms, such as a mammal.

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- 70. A fluorescent probe comprising a GFP which is N- or C-terminally tagged, optionally via a peptide linker, to a biologically active polypeptide or a part or a subunit thereof which is a component of a intracellular signalling pathway as defined herein, the probe being a probe which is encoded by the nucleic acid construct according to any of claims 40-59.
- 71. A method according to any of claims 1-39, wherein the luminophore is a fusion polypeptide as encoded by the nucleic acid construct according to any of claims 40-63.
- 72. A method according to any of claims 1-39 or 71 in which the method of the invention is used in a screening program as defined herein.
 - 73. An apparatus for measuring the distribution of fluorescence in at least one cell, and thereby any change in the distribution of fluorescence in at least one cell, which includes the following component parts: (a) a light source, (b) a means for selecting the wavelength(s) of light from the source which will excite the fluorescence of the protein, (c) a means for rapidly blocking or pass ing the excitation light into the rest of the system, (d) a series of optical elements for conveying the excitation light to the specimen, collecting the emitted fluorescence in a spatially resolved fashion, and forming an image from this fluorescence, (e) a bench or stand which holds the container of the cells being measured in a predetermined geometry with respect to the series of optical elements, (f) a detector to record the spatially resolved fluorescence in the form of an image, (g) a computer or electronic system and associated software to acquire and store the recorded images, and to compute the degree of redistribution from the recorded images.

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- 74. An apparatus according to claim 73 in which some or all of the system is automated.
- 75. An apparatus according to claim 73 in which components d and e comprise a fluorescence microscope.

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76. An apparatus according to claim 73 in which component f is a CCD camera.

77. An apparatus according to claim 73 in which the image is formed and recorded by an optical scanning system.

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- 78. An apparatus according to claim 73 in which a liquid addition system is used to add a known or unknown compound to any or all of the cells in the cell holder at a time determined in advance.
- 79. An apparatus according to claim 78 in which the liquid addition system is under the control of the computer or electronic system.
 - 80. A method according to any of claims 1-79 wherein the method is a screening program for the identification of a biologically active substance as defined herein that directly or indirectly affects an intracellular signalling pathway and is potentially useful as a medicament, wherein the result of the individual measurement of each substance being screened which indicates its potential biological activity is based on measurement of the redistribution of spatially resolved luminescence in living cells and which undergoes a change in distribution upon activation of an intracellular signalling pathway.

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- 81 A method according to any of claims 1-79 wherein the method is a screening program for the identification of a biologically toxic substance as defined herein that exerts its toxic effect by interfering with an intracellular signalling pathway, wherein the result of the individual measurement of each substance being screened which indicates its potential biologically toxic activity is based on measurement of the redistribution of said fluorescent probe in living cells and which undergoes a change in distribution upon activation of an intracellular signalling pathway.
- 82. A method according to any of claims 1-80 wherein a fluorescent probe is used in back tracking of signal transduction pathways as defined herein.

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- 83. A method of treating a condition or disease related to the intracellular function of a protein kinase comprising administering to a patient suffering from said condition or disease an effective amount of a compound which has been discovered by any method according to the invention.
- 84. A compound that modulates a component of an intracellular pathway as defined herein, as determined by a method according to the method of the invention.
- 10 85. A medical composition comprising a therapeutic amount of a compound identified according the method of the invention.

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- 86. A method of selectively treating a patient suffering from an ailment which responds to medical treatment comprising obtaining a primary cell or cells from said patient, transfecting the cell or cells with at least one DNA sequence encoding a fluorescent probe according to the invention, culturing the cell or cells under conditions permitting the expression of said probes and exposing it to an array of medicaments suspected of being capable of alleviating said ailment, then comparing changes in fluorescence patterns or redistribution patterns of the fluorescent probes in the intact living cell or cells to detect the cellular response to the specific medicaments (obtaining a cellular action profile), then selecting a medicament(s) based on desired activity and acceptable level of side effects and administering an effective amount of said medicament(s) to said patient.
- 87. A method according to any of claims 1-80 of identifying a drug target among the group of biologically active polypeptides which are components of intracellular signalling pathways.

Fig 1

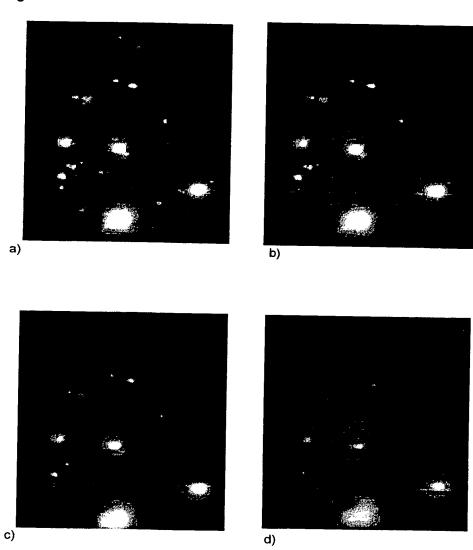


Fig 2

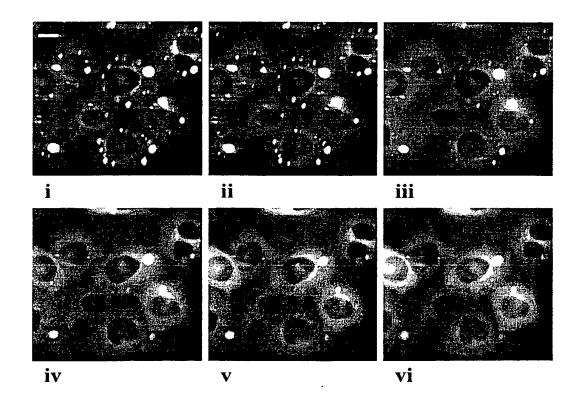
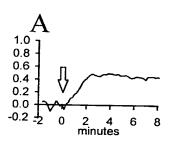
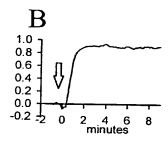
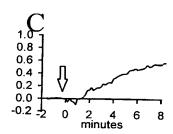
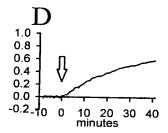


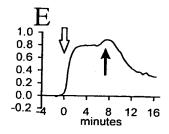
Fig 3

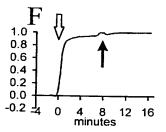


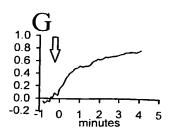


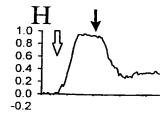






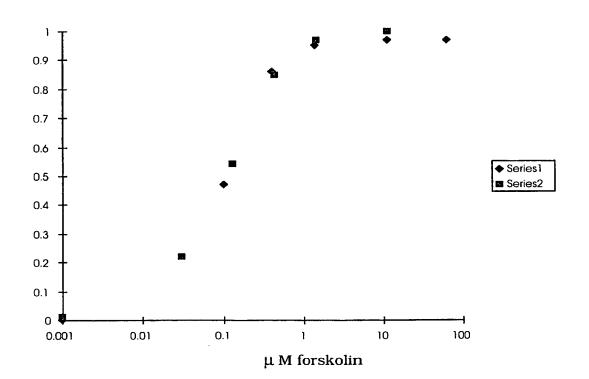






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Fig 4

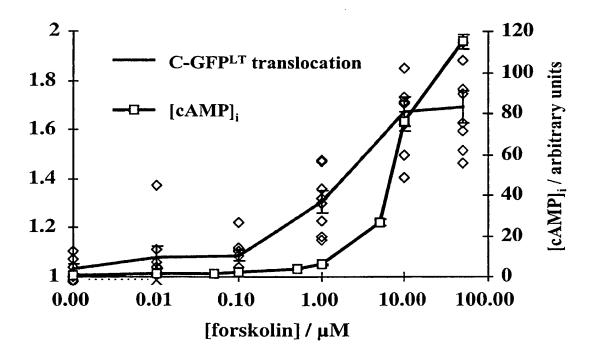


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Fig 5

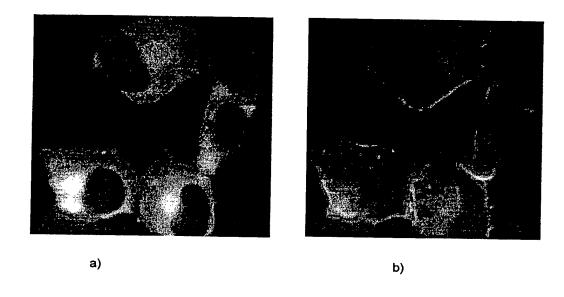
[forskolin]µM	$t_{1/2\text{max}}/s$	t _{max} /s
1	115±21	310±31
10	69±14	224±47
50	47±10	125±28

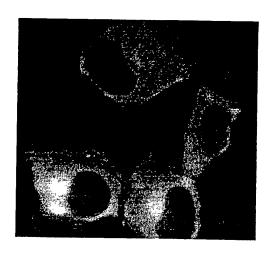
Fig 6



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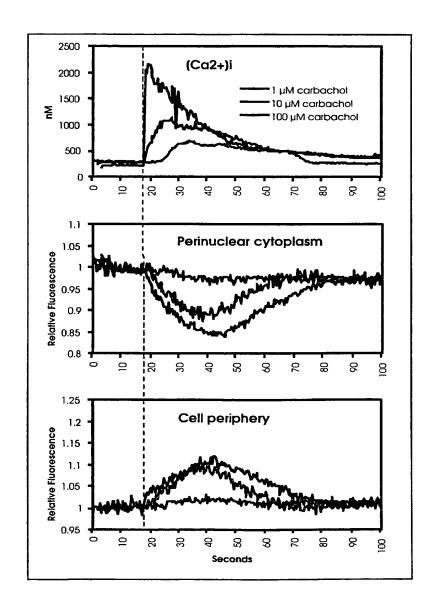
Fig 7



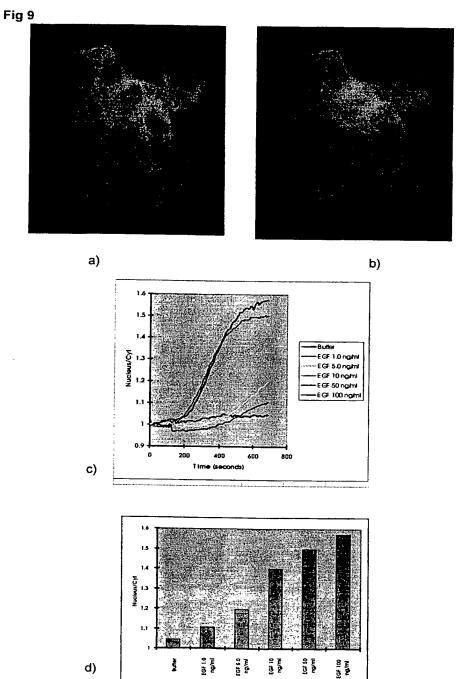


c)

Fig 8



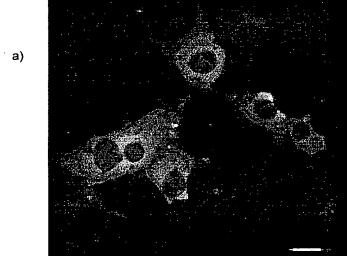


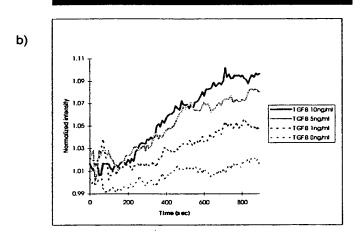


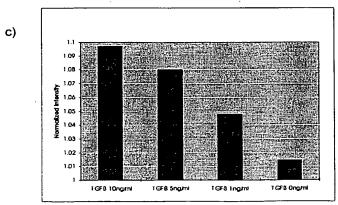
WO 98/45704 PCT/DK98/00145







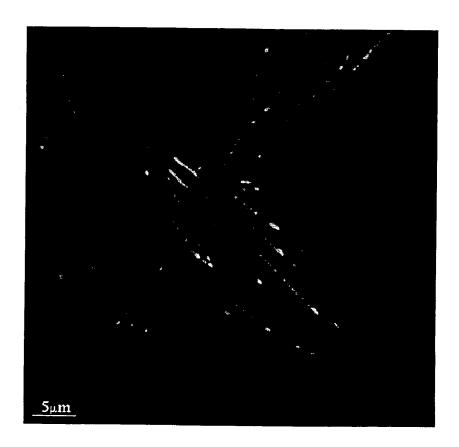




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Fig 11

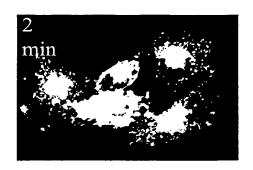


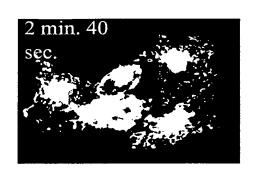
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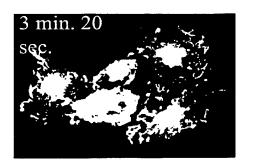
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Fig. 12













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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/DK98 (22) International Filing Date: 7 April 1998 (07 (30) Priority Data: 0392/97 7 April 1997 (07.04.97) (71) Applicant (for all designated States except US): NORDISK A/S [DK/DK]; Novo Allé, DK-2880 Bag (DK). (72) Inventors; and (75) Inventors/Applicants (for US only): THASTRUP [DK/DK]; Birkevej 37, DK-3460 Birkerød (DK TERSEN BJØRN, Sara [DK/DK]; Klampenborgve DK-2800 Lyngby (DK). TULLIN, Søren [DK/DK] Gjellerups Alle 18, DK-2860 Søborg (DK). KA Almholt [DK/DK]; Eigilsgade 32, 4. tv, DK-2300 khavn S (DK). SCUDDER, Kurt [US/DK]; Lavendel 70, DK-2830 Virum (DK). (74) Common Representative: NOVO NORDISK A/S; attn Kellberg, Novo Allé, DK-2880 Bagsværd (DK).	NOVO gsvaero P, Ole). PE ej 102 j; Kar SPER Køben-	BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPC patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments. (88) Date of publication of the international search report: 22 April 1999 (22.04.99)

(54) Title: A METHOD FOR EXTRACTING QUANTITATIVE INFORMATION RELATING TO AN INFLUENCE ON A CELLULAR RESPONSE

(57) Abstract

Cells are genetically modified to expresss a luminophore, e.g., a modified (F64L, S65T, Y66H) Green Fluorescent Protein (GFP, EGFP) coupled to a component of an intracellular signalling pathway such as a transcription factor, a cGMP- or cAMP-dependent protein kinase, a cyclin-, calmodulin- or phospholipid-dependent or mitogen-activated serine/threonin protein kinase, a tyrosine protein kinase, or a protein phosphatase (e.g. PKA, PKC, Erk, Smad, VASP, actin, p38, Jnk1, PKG, IkappaB, CDK2, Grk5, Zap70, p85, protein-tyrosine phosphatase 1C, Stat5, NFAT, NFkappaB, RhoA, PKB). An influence modulates the intracellular signalling pathway in such a way that the luminophore is being redistributed or translocated with the component in living cells in a manner experimentally determined to be correlated to the degree of the influence. Measurement of redistribution is performed by recording of light intensity, fluorescence lifetime, polarization, wavelength shift, resonance energy transfer, or other properties by an apparatus consisting of e.g. a fluorescence microscope and a CCD camera. Data stored as digital images are processed to numbers representing the degree of redistribution. The method can be used as a screening program for identifying a compound that modulates a component and is capable of treating a disease related to the function of the component.

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Int. tional Application No PCT/DK 98/00145

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C. DOCUM	ENTS CONSIDERED TO BE RELEVANT			
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Y	see the whole document see claims		64-82,88 28,29, 41,61-63	
X	WO 91 01305 A (UNIV WALES MEDIC) 7 February 1991	INE)	1-27, 30-40, 42-60, 64-84,	
Υ	see page 4, line 15 - line 20 see claims see examples 1-10		87,88 28,29, 41,61-63	
	See examples 1 10	-/		
	er documents are listed in the continuation of box C.	X Patent family me	mbers are listed in annex.	
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	ation) DOCUMENTS CONSIDERED TO BE RELEVANT	I Polovica the states Ma
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Υ	see claim 26 see the whole document	28,29, 41,61-63
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	ation) DOCUMENTS CONSIDERED TO BE RELEVANT	
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tr. ational application No. PCT/DK 98/00145

Box I	Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)
This Inte	ernational Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
1. X	Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
2. X	Although claims 83-84 and claim 87 relate to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition (Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy). Claims Nos.: 85,86
	because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
	see FURTHER INFORMATION sheet PCT/ISA/210
3.	Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box II	Observations where unity of invention is lacking (Continuation of item 2 of first sheet)
This Inter	rnational Searching Authority found multiple inventions in this international application, as follows:
	see additional sheet
1. X	As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2	As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3	As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.	No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is estricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Remark o	The additional search fees were accompanied by the applicant's protest. No protest accompanied the payment of additional search fees.

International Application No. PCT/DK 98/00145

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Claims Nos.: 85,86

The subject-matter (compounds per se) is solely characterised in claims 85 and 86 by the result to be achieved, no support of a technical character is derivable from the description for the technical formulation of the subject of the search, accordingly no scope of a search could be defined and a meaningfull search is hence not possible.

International Application No. PCT/DK 98/00145

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: Partially: 1-43, 46, 59-82 and 88; Entirely: 47, 49, 53-57

Methods for extracting information from influences on a living cell involving observing spatial redistribution or modulation of a luminophore linked to a biologically active molecule, in particular to a molecule involved in intracellular signalling pathways, nucleic acids encoding fusion proteins comprising bothe the luminophore and the biological active molecule, cells containing and expressing these nucleic acids, as well as methods and apparatuses involving above products, inso far as related to the biologically active protein being serine/threonine protein kinases

2. Claims: Partially: 1-41, 43, 59-82 and 88; Entirely: 48

Methods for extracting information from influences on a living cell involving observing spatial redistribution or modulation of a luminophore linked to a biologically active molecule, in particular to a molecule involved in intracellular signalling pathways, nucleic acids encoding fusion proteins comprising bothe the luminophore and the biological active molecule, cells containing and expressing these nucleic acids, as well as methods and apparatuses involving above products, inso far as related to the biologically active protein being to tyrosine kinases

3. Claims: Partially: 1-43, 46, 59-82 and 88; Entirely: 50, 51

MMethods for extracting information from influences on a living cell involving observing spatial redistribution or modulation of a luminophore linked to a biologically active molecule, in particular to a molecule involved in intracellular signalling pathways, nucleic acids encoding fusion proteins comprising bothe the luminophore and the biological active molecule, cells containing and expressing these nucleic acids, as well as methods and apparatuses involving above products, inso far as related to the biologically active protein being to cAMP dependent protein kinases.

4. Claims: Partially: 1-43, 46, 59-82 and 88; Entirely: 52

MMethods for extracting information from influences on a living cell involving observing spatial redistribution or modulation of a luminophore linked to a biologically active

International Application No. PCT/DK 98/00145

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

molecule, in particular to a molecule involved in intracellular signalling pathways, nucleic acids encoding fusion proteins comprising bothe the luminophore and the biological active molecule, cells containing and expressing these nucleic acids, as well as methods and apparatuses involving above products, inso far as related to the biologically active protein being cGMP dependent protein kinases

5. Claims: Partially: 1-43, 59-82 and 88; Entirely: 58

Methods for extracting information from influences on a living cell involving observing spatial redistribution or modulation of a luminophore linked to a biologically active molecule, in particular to a molecule involved in intracellular signalling pathways, nucleic acids encoding fusion proteins comprising bothe the luminophore and the biological active molecule, cells containing and expressing these nucleic acids, as well as methods and apparatuses involving above products, inso far as related to the biologically active protein being protein phosphatases

6. Claims: Partially: 1-41, 43, 59-82 and 88; Entirely: 44

Methods for extracting information from influences on a living cell involving observing spatial redistribution or modulation of a luminophore linked to a biologically active molecule, in particular to a molecule involved in intracellular signalling pathways, nucleic acids encoding fusion proteins comprising bothe the luminophore and the biological active molecule, cells containing and expressing these nucleic acids, as well as methods and apparatuses involving above products, inso far as related to the biologically active protein being to transcription factors

7. Claims: Partially: 1-41, 43, 59-82 and 88; Entirely: 45

Methods for extracting information from influences on a living cell involving observing spatial redistribution or modulation of a luminophore linked to a biologically active molecule, in particular to a molecule involved in intracellular signalling pathways, nucleic acids encoding fusion proteins comprising bothe the luminophore and the biological active molecule, cells containing and expressing these nucleic acids, as well as methods and apparatuses involving above products, inso far as related to the biologically active protein being to proteins associated with the cytoskeletal network



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